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Myocardial Imaging for Coronary Artery Disease

Review on TQ-ST Segment Mapping: Current Concepts

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A YORKE MEDICAL JOURNAL

in hypertension

ALDOMET® 500 mg

(METHYLDOPA | MSD) 500-mg TABLETS



OFFERS B.I.D. CONVENIENCE WHEN HIGHER DOSAGE IS INDICATED

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- **Why convenient.** A b.i.d. schedule with ALDOMET 500-mg tablets may mean fewer doses a day for the patient and fewer tablets per dose. This convenience helps encourage patient compliance with the regimen. (Please see Addendum on following page for more information on dosage.)

ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

For more details see the brief summary of prescribing information.

MSD
MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

ALDOMET®
(METHYLDOPA | MSD)

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

P24,117

DOSAGE INFORMATION ON ALDOMET® (Methyldopa | MSD)

Adults

initiating therapy

- 250 mg b.i.d. or t.i.d. the first 48 hours
- increase or decrease, preferably at intervals of not less than two days, until response is adequate
- start dosage increases in the evening to minimize sedation
- adjusting dosage may prevent morning hypotension without losing control of afternoon blood pressure
- when ALDOMET is added, the dosage of thiazides need not be changed
- when given with antihypertensives other than thiazides, the dose of these agents may have to be adjusted and the starting dosage of ALDOMET should be limited to 500 mg daily in divided doses

maintaining therapy

- usually 500 mg to 2.0 g daily in two to four doses
- maximum recommended daily dose is 3.0 g
- occasional tolerance may occur, usually between the second and third month of therapy; adding a diuretic or increasing the dosage of ALDOMET frequently restores effective control
- patients with impaired renal function may respond to lower doses; syncope in older patients may be related to an increased sensitivity and advanced arteriosclerotic vascular disease and may be avoided by lower doses

Children

- initial dosage is based on 10 mg/kg of body weight daily in two to four doses
- increase or decrease daily dosage until adequate response is achieved
- maximum dosage is 65 mg/kg or 3.0 g daily, whichever is less

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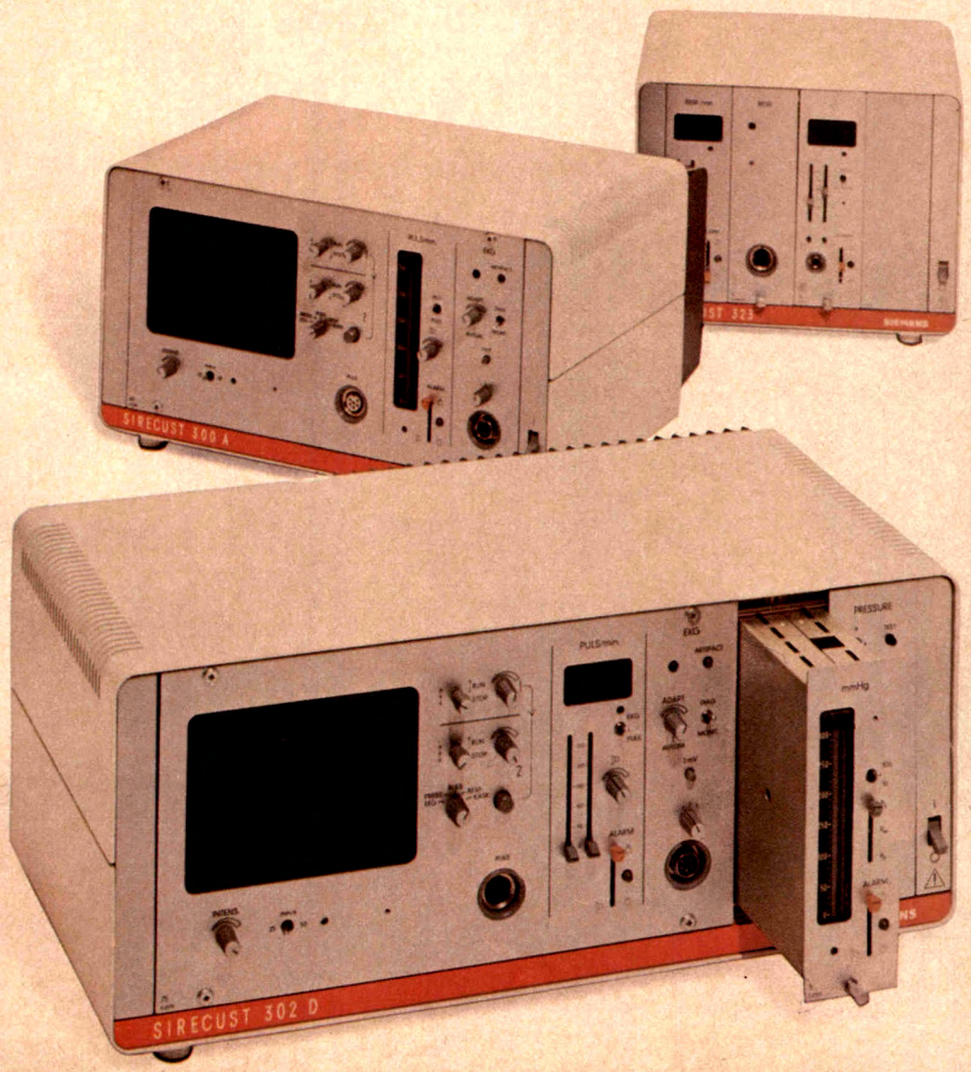
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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome, steroid induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism; to increase diuresis in patients resistant to other diuretics. Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy when edema is due to pathological causes (see Warnings).

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

SK&F CO. Carolina, P.R. 00630

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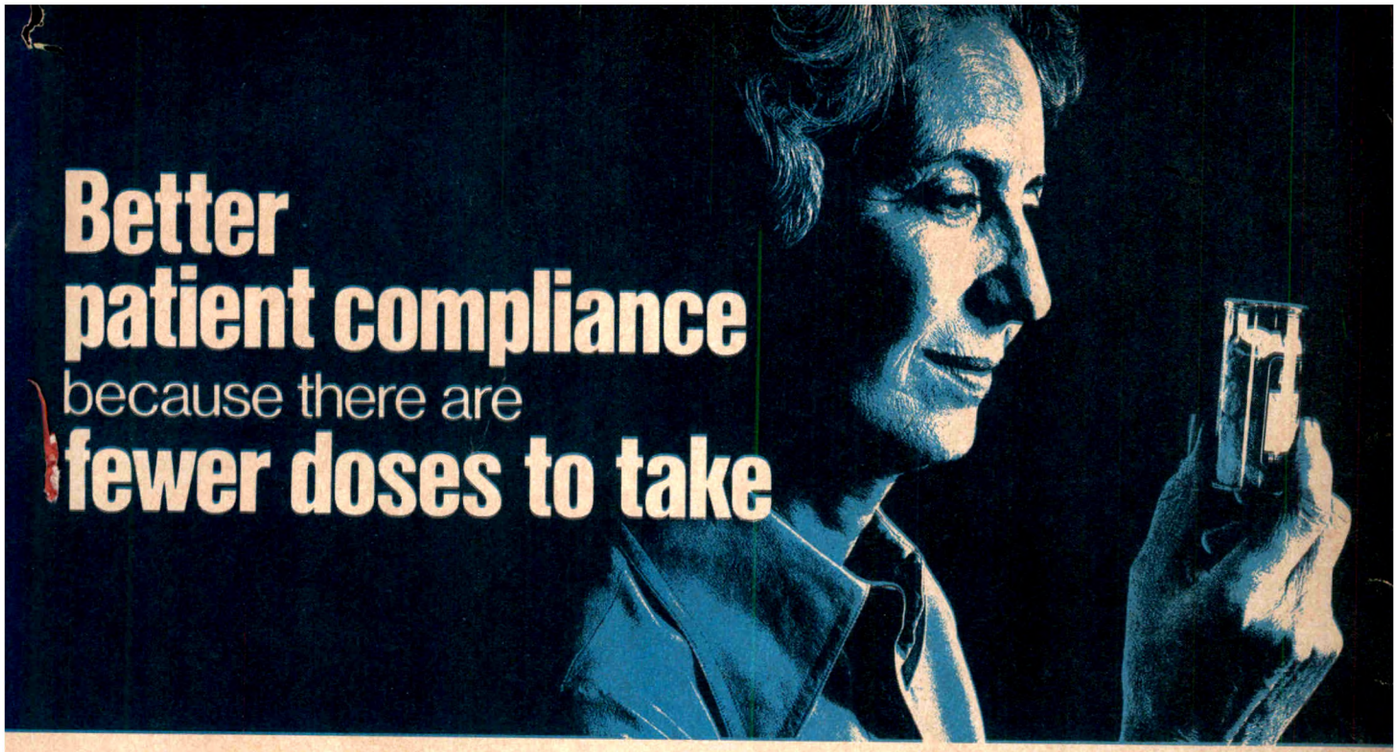
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Premature atrial and ventricular contractions. Paroxysmal atrial tachycardia. Paroxysmal A-V junctional rhythm. Atrial flutter. Paroxysmal atrial fibrillation. Established atrial fibrillation when therapy is appropriate. Paroxysmal ventricular tachycardia when not associated with complete heart block. Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.
NOTE: Depending upon the response desired, the dosage may need to be varied and the blood level and/or electrocardiographic response closely monitored during initial treatment.

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.

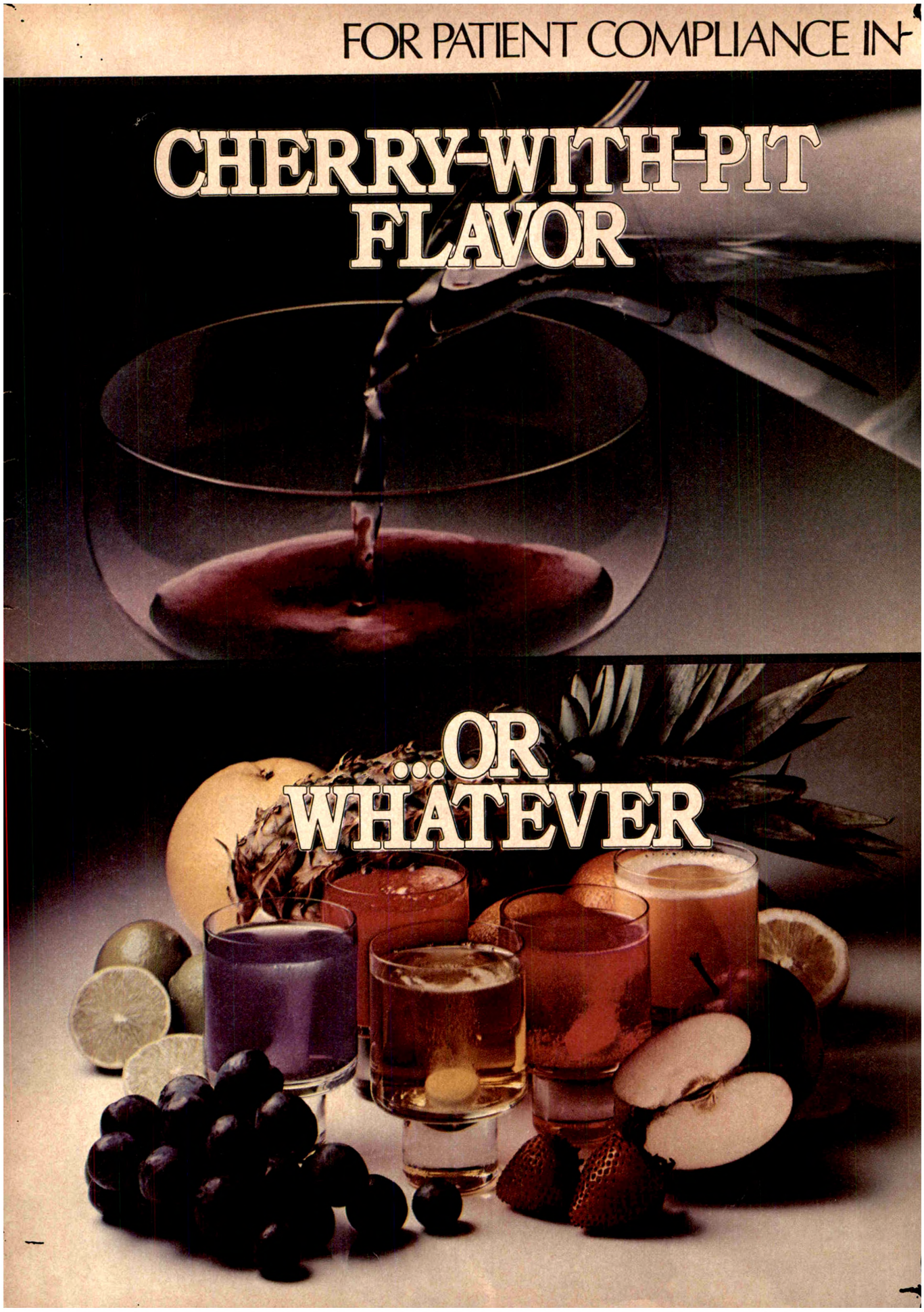
It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

101-48

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FOR PATIENT COMPLIANCE IN-



OTASSIUM SUPPLEMENTATION

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Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable cherry-with-pit flavored vehicle, alcohol 1%.

Delicious cherry-with-pit flavor. If you've tasted it, you know KLORVESS® (potassium chloride) 10% Liquid provides a delicious natural flavor. So good, in fact, that it should be mixed only with water.

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Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g.

Or whatever flavor your patients like . . . because the taste of KLORVESS® Effervescent Tablets is determined by what they're mixed with. The subtle mixer.

Convenience in therapeutic doses. Both forms of KLORVESS offer 20 mEq of potassium and chloride in each dose. There is no need to prescribe several slow-release tablets per dose or space dosage administration beyond the patient's normal routine. Prescribe KLORVESS Liquid or KLORVESS Effervescent Tablets . . . for potassium supplement therapy that offers good taste and convenience at therapeutic dosages.

Description: Klorvess Effervescent Tablets: Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g. Dissolution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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BD--B

JULY 1977

The American Journal of CARDIOLOGY®

VOLUME 40

NUMBER 1

CONTENTS

CLINICAL STUDIES

1 **Technetium-99m Pyrophosphate Myocardial Uptake in Patients With Stable Angina Pectoris**

JAY W. MASON, RICHARD W. MYERS, EDWIN L. ALDERMAN, EDWARD B. STINSON, MICHAEL L. GORIS and JOSEPH P. KRISS

A new scoring method that averaged the interpretations of four observers using blinded reading techniques was utilized to minimize observer error and interobserver disagreement in evaluating myocardial scintigraphic results. This study of 55 patients with stable angina pectoris and 13 normal subjects demonstrated excess accumulation of 99m-Tc pyrophosphate in those with angina and a higher mean scintigraphic grade in those with a prior myocardial infarction. In the subjects with stable angina, pyrophosphate uptake was diffuse in 70 percent of the 51 scintigrams with detectable uptake. Three of the 68 subjects had high levels of radionuclide uptake without clinical evidence of acute myocardial injury, thus indicating that pyrophosphate scintigraphy is not a completely specific test for acute myocardial infarction.

6 **Diagnostic Accuracy of Noninvasive Myocardial Imaging for Coronary Artery Disease: An Electrocardiographic and Angiographic Correlation**

RONALD L. McGOWAN, NEIL D. MARTIN, BARRY L. ZARET, RONALD R. HALL, A. LAIRD BRYSON, H. WILLIAM STRAUSS and M. DANIEL FLAMM

In this study of 160 patients who had myocardial imaging, stress electrocardiography and angiography performed for coronary artery disease, noninvasive myocardial imaging proved safe, produced no untoward side effects and required only a small radiation dose. Its good overall sensitivity rate (83 percent) was comparable with the 80 percent sensitivity rate of electrocardiographic stress testing. The specificity rate was 82 percent for myocardial imaging but only 50 percent for electrocardiographic testing. The sensitivity rate in identifying significant coronary artery disease when combining the results of noninvasive myocardial imaging with electrocardiographic findings was 92 percent, but frequent false positive tests reduced the specificity rate to less than 50 percent when these results were combined. It is expected that recent changes in techniques will improve the diagnostic accuracy of noninvasive myocardial imaging.

11 **Echocardiographic Diagnosis of Left Anterior Descending Coronary Artery Disease**

C. DAVID JOFFE, HENRY BRIK, LOUIS EVAN TEICHHOLZ, MICHAEL V. HERMAN and RICHARD GORLIN

Because the blood supply to the muscular septum of the heart derives primarily from branches of the left anterior descending coronary artery, it is not unexpected that abnormalities of septal motion should be found associated with disease of that artery. In this study of 77 patients with a chest pain syndrome, abnormal septal motion, as measured with

Continued on page A12

IN PREDICTABLE ANGINA*



...during the postprandial period

SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Probably" effective: The chewable dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classifications of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing, transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: *Individual Dose:* To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg., the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

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the posterior wall/interventricular excursion ratio in the echocardiogram, proved a useful index for the diagnosis of disease of the left anterior descending coronary artery when that disease is proximal to the first septal branch. Proximal disease was found in 79 percent of patients with abnormal septal motion in the echocardiogram (15 to 19) but in only 7 percent of those with normal septal motion (4 of 58).

17 **Echocardiographic Observations in Opiate Addicts With Active Infective Endocarditis. Frequency of Involvement of the Various Valves and Comparison of Echocardiographic Features of Right- and Left-Sided Cardiac Valve Endocarditis**

JOSEPH J. ANDY, MAZHAR U. SHEIKH, NAYAB ALI, BOISEY O. BARNES, LAY M. FOX, CHARLES L. CURRY and WILLIAM C. ROBERTS

Echocardiographic observations in 25 opiate addicts with active infective endocarditis involving apparently previously normal valves showed abnormalities consistent with active infective endocarditis in 75 percent of 35 clinically incompetent valves but in none of the 40 competent valves. The echocardiogram was less sensitive in detecting tricuspid valve lesions. Rupture of tricuspid valve chordae tendineae was absent or not detectable and tricuspid valve vegetations tended to be larger. The mitral and aortic valves were well visualized with the echocardiogram in all 25 patients, and the tricuspid valve was well seen in 22. The echocardiogram of the pulmonary valve recorded in 12 patients detected no lesions of active infective endocarditis.

24 **Mode of Initiation of Reciprocating Tachycardia During Programmed Ventricular Stimulation in the Wolff-Parkinson-White Syndrome. With Reference to Various Patterns of Ventriculoatrial Conduction**

RUEY J. SUNG, AGUSTIN CASTELLANOS, STEPHEN M. MALLON, HENRY GELBAND, IVAN MENDOZA and ROBERT J. MYERBURG

This study of 29 patients with Wolff-Parkinson-White (WPW) syndrome, type A demonstrates the importance of differences in the electrophysiologic properties of the two atrioventricular (A-V) conduction pathways (the normal pathway and the accessory pathway) in the genesis of reciprocating tachycardia. The initiation of reciprocating tachycardia during programmed ventricular stimulation is related to various patterns of ventriculoatrial (V-A) conduction. Except in patients without V-A conduction, the initiation of reciprocating tachycardia generally depends on the depth of retrograde penetration of the normal pathway induced by premature ventricular beats. The less this depth, the more easily can reciprocating tachycardia be elicited.

32 **Chronic Recurrent Right and Left Ventricular Tachycardia: Comparison of Clinical, Hemodynamic and Angiographic Findings**

RAYMOND J. PIETRAS, RICHARD MAUTNER, PABLO DENES, DELON WU, RAMESH DHINGRA, WILLIAM TOWNE and KENNETH M. ROSEN

These results suggest that chronic recurrent right and left ventricular tachycardias have different clinical significance. In this study 15 patients with left ventricular tachycardia were older, predominantly male, had diagnosable organic heart disease, lower cardiac output and a much greater prevalence of abnormal left ventricular and coronary angiograms than the 12 patients with right ventricular tachycardia. Three patients with left but none

Continued on page A17

PC

Time is the test of all things.

1954
1977



BRIEF SUMMARY

Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. May be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.

Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation.

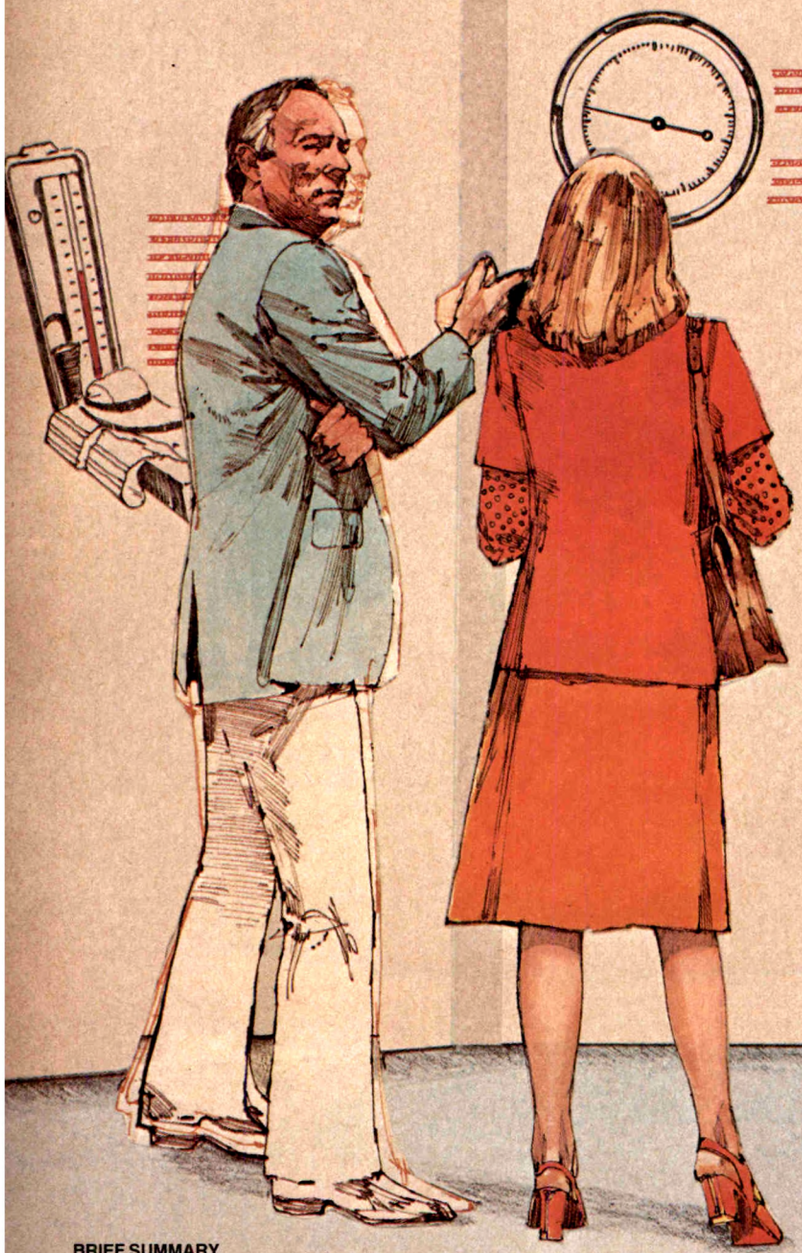
Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The most severe adverse effect is hyperkalemia.

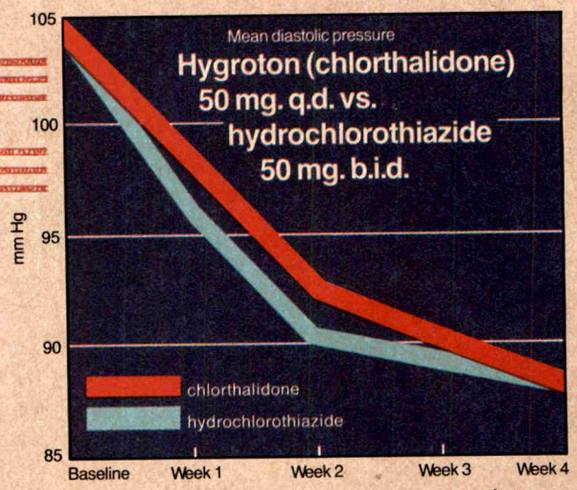
Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications". Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

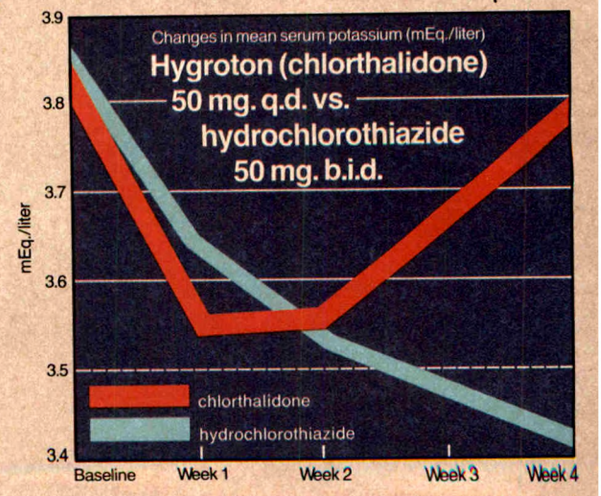
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(Charts from Finnerty.[1])

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

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References: 1. Finnerty, F. A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20–23, 1976. 2. Baer, L.: Hypertension: A Physiologic Approach to Management, New York, Medcom, 1976, p. 9. 3. Finnerty, F. A., Jr.: Mild and moderate hypertension, in Hypertensive Management for the Practicing Physician (Finnerty, F. A., Jr., ed.), New York, Medcom, 1974, p. 14.

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with right ventricular tachycardia died. Mortality is primarily influenced by the presence of underlying organic heart disease rather than by arrhythmia. Although the site of origin of ventricular ectopic beats can be easily identified clinically from the QRS configuration in the electrocardiogram, epicardial mapping provides the most definitive means of documenting the site of origin of ventricular tachycardia.

EXPERIMENTAL STUDIES

38 Direct and Reflex Cardiostimulating Effects of Hydralazine

IBRAHIM KHATRI, NOBUHIRO UEMURA, ALDO NOTARGIACOMO and EDWARD D. FREIS

These dog experiments indicate that the cardiostimulatory effect of hydralazine is due not only to reflex activation of the sympathetic nervous system secondary to the decrease in blood pressure but also to direct inotropic and chronotropic action on the myocardium due to beta adrenergic stimulation. After intravenous injection of hydralazine, 20 mg, myocardial contractile force increased on average by 27 percent and heart rate by 7 percent; mean arterial pressure decreased less than 10 percent. The same reduction of mean arterial pressure with sodium nitroprusside increased myocardial contractile force only 10 percent and heart rate 2 percent. Direct injections of hydralazine into a coronary artery in four dogs consistently increased myocardial contractile force in the area perfused. The intravenous administration of propranolol blocked the local effect of hydralazine. The administration of sodium nitroprusside exerted no such local inotropic activity.

43 Effect of Hyaluronidase During the Early Phase of Acute Myocardial Ischemia: An Ultrastructural and Morphometric Analysis

ROBERT A. KLONER, MICHAEL C. FISHBEIN, DEREK MACLEAN, EUGENE BRAUNWALD and PETER R. MAROKO

These results in rats suggest that hyaluronidase decreases ischemic injury to myocardial and endothelial cells during the early phase of coronary occlusion, protects the microvasculature and preserves myocardial glycogen granules. The preservation of collateral flow may be a secondary mode by which hyaluronidase decreases infarct size. Morphometric analysis of tissues taken from comparable anatomic sites of the ischemic anterior left ventricular wall 3 hours after occlusion showed that in untreated rats 80 ± 7 percent of myocardial cells and 48 ± 8 percent of vessels had morphologic evidence of ischemic damage compared with 50 ± 10 percent and 24 ± 6 percent, respectively, in rats treated with hyaluronidase. Ultrastructurally, more glycogen granules were present in the treated group, suggesting that hyaluronidase may decrease infarct size by improving substrate delivery.

50 Electrophysiologic Effects of Partial Coronary Occlusion and Reperfusion

KODANGUDI B. RAMANATHAN, MONTY M. BODENHEIMER, VIDYA S. BANKA and RICHARD H. HELFANT

These electrophysiologic studies in dogs show that partial coronary occlusion significantly shortens refractoriness in the ischemic zone; this begins within minutes and lasts for the duration of the partial coronary occlusion, which results in an inhomogeneity of ventricular refractoriness between the ischemic and the nonischemic zone. After a 50 percent reduction in coronary blood flow, the decrease in local refractory period and prolongation of conduction time lead to underlying electrical instability predisposing to reentrant arrhythmias whereas automaticity is unchanged. Reperfusion instituted after 60 minutes of partial coronary occlusion fully abolished these abnormalities in contrast to reperfusion after total coronary occlusion, which has been shown to be intensively arrhythmogenic.

Continued on page A18

CONTENTS

METHODS

55 Effects of Pacing-Induced Myocardial Ischemia on Hypoxanthine Efflux From the Human Heart

WILLIAM J. REMME, JAN WILLEM de JONG and PIETER D. VERDOUW

Sudden hypoxia at the cell level within seconds causes increased anaerobiosis and a precipitous decrease in the high energy compound creatine phosphate, which is followed by a breakdown of adenosine triphosphate (ATP). The enhanced degradation of ATP increases efflux of the breakdown products able to pass the cell membrane—inorganic phosphate, adenosine, inosine and hypoxanthine. This study shows that release of hypoxanthine is a useful indicator of pacing-induced ischemia in the human heart. Such pacing-induced myocardial ischemia elevated coronary sinus hypoxanthine levels only after the onset of angina in 18 patients, whereas lactate production often occurred before angina was noted. The simultaneous measurement of hypoxanthine and lactate provides additional information about abnormal myocardial metabolism.

63 New Endomyocardial Biopsy Catheter for the Left Ventricle

CHUICHI KAWAI and YASUSHI KITAURA

A new biopsy catheter with a flexible tip specifically made for left ventricular endomyocardial biopsy proved highly successful in 12 dogs and in five patients with cardiomyopathy. Entering the left ventricle was easier in patients than in dogs, and only a few premature ventricular contractions were noted at the time of contact of the tip with the left ventricular endocardium and of excision of the biopsy specimens. There were no serious complications.

PEDIATRIC CARDIOLOGY

66 Surgical Correction of Atrioventricular Canal During the First Year of Life

DOUGLAS D. MAIR and DWIGHT C. McGOON

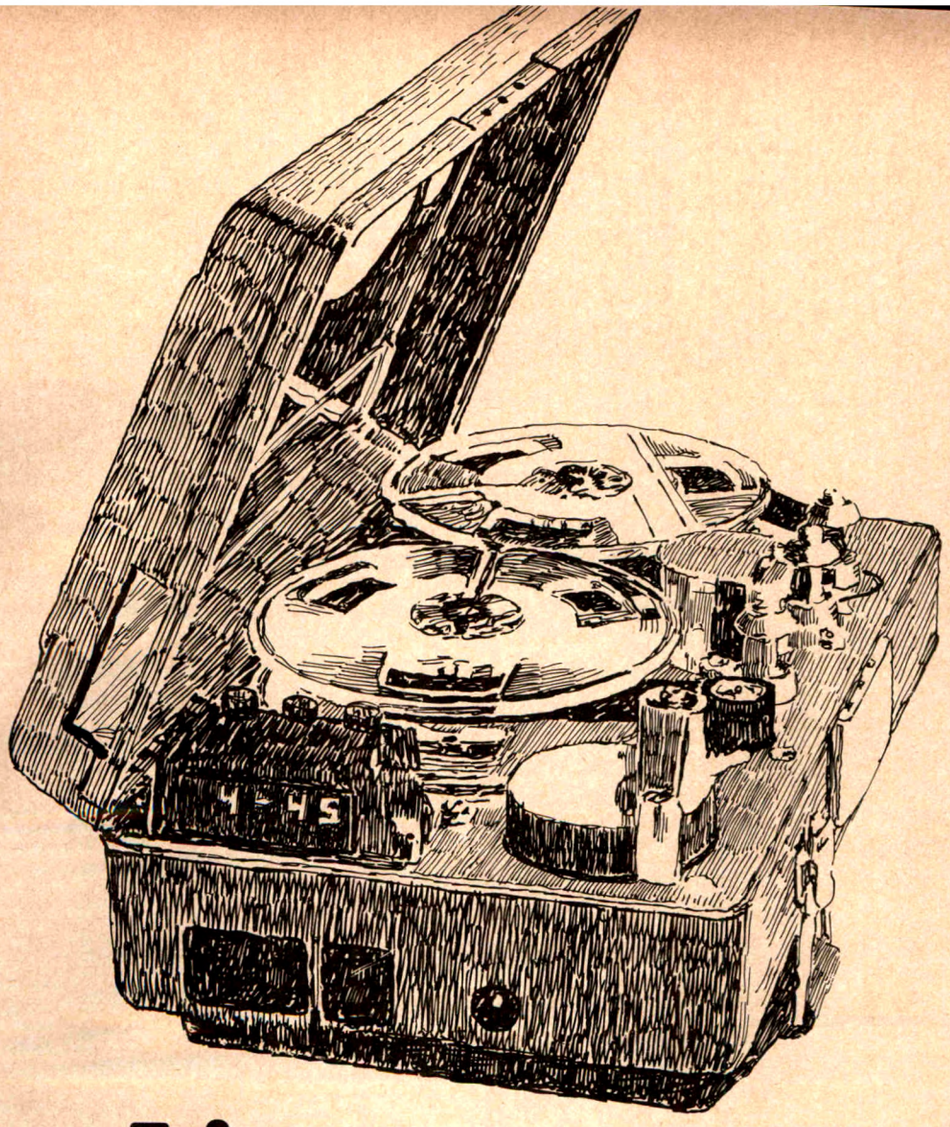
Early elective definitive correction of atrioventricular canal defect is desirable in patients with this lesion and severe pulmonary hypertension during the first 1 or 2 years of life, especially since no effective surgical palliation is really available. Good operative results have been achieved for nearly a decade in older patients with this lesion and this article reports similar results in infants. Definitive surgical correction was successfully achieved in 6 of 8 infants less than 1 year of age with intractable congestive heart failure. Cardiac catheterization in one survivor 2 1/2 years after operation showed mild mitral incompetence with a very small residual left to right shunt at the atrial level, a mean pulmonary arterial wedge pressure of 14 mm Hg and a pulmonary arterial pressure of 34/16 mm Hg.

70 Congenital Pulmonary Atresia With Tricuspid Insufficiency: Morphologic Study

SAROJA BHARATI, HUGH A. McALLISTER, Jr., PIPIT CHEMMONGKOLTIP and MAURICE LEV

Great morphologic differences exist between pulmonary atresia with intact ventricular septum, type I (with tricuspid stenosis and a small right ventricle) and type II (with tricuspid insufficiency and a large right ventricle) as shown in this anatomic study of 21 cases of pulmonary atresia with tricuspid insufficiency. At the Congenital Heart Disease Research and Training Center in Chicago, pulmonary atresia with tricuspid insufficiency was a relatively rare anomaly. It may be more amenable to surgery than pulmonary atresia with tricuspid

Continued on page A20



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stenosis because the right ventricle in the former may be converted into a functional chamber by a valvotomy combined with a shunting procedure and atrial septostomy. It is difficult to separate this entity from Ebstein's disease when part of the medial leaflet is absent and fragments of the valve are found more distally in the right ventricle.

REPORTS ON THERAPY

76 **Altered Hemoglobin-Oxygen Affinity With Long-Term Propranolol Therapy in Patients With Coronary Artery Disease**

JOHN D. SCHRUMPF, DAVID S. SHEPS, STEVEN WOLFSON, ALFRED L. ARONSON and LAWRENCE S. COHEN

Orally administered propranolol shifted the oxyhemoglobin equilibrium curve to the right without changing erythrocyte 2,3-diphosphoglycerate in 12 patients with moderate to severe angina pectoris. The mean P_{50} after discontinuation of propranolol was 28.1 ± 0.9 mm Hg and during propranolol therapy 31.6 ± 0.7. This demonstrated shift may increase tissue oxygen delivery and benefit marginally perfused myocardium while sparing coronary flow in patients with angina pectoris. In seven patients who performed exercise tests the larger increases in P_{50} were associated with increased exercise tolerance while they took propranolol. These studies present the possibility of a new pharmacologic approach to clinical states manifested by ischemia.

83 **Effects of Propranolol on the Hemodynamic, Coronary Sinus Blood Flow and Myocardial Metabolic Response to Atrial Pacing**

PAUL W. ARMSTRONG, MIGUEL A. CHIONG and JOHN O. PARKER

This study in 19 patients with coronary artery disease and 6 normal patients demonstrates that propranolol can favorably influence the anginal threshold, as assessed with atrial pacing, independent of global changes in coronary sinus blood flow and myocardial oxygen consumption. After propranolol, clinical improvement occurred in 9 of the 15 patients who had angina during the initial pacing period. This improvement was associated with less severe S-T depression and no significant change in coronary sinus blood flow or myocardial oxygen consumption. Those who did not respond favorably may have had more advanced coronary artery disease, as evidenced by the lower pacing rate required to achieve angina and abnormal resting lactate metabolism. After propranolol, the left ventricular end-diastolic pressure decreased during pacing in the group with improvement and increased in the group without improvement, but there was no change in the post-pacing left ventricular end-diastolic pressure in the former group.

90 **Prolonged Salutary Effects of Isosorbide Dinitrate and Nitroglycerin Ointment on Regional Left Ventricular Function**

THORDUR HARDARSON, HARTMUT HENNING and ROBERT A. O'ROURKE

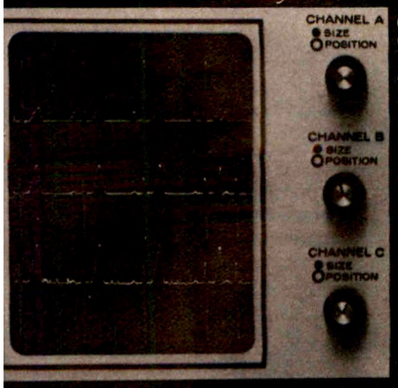
The oral administration of isosorbide dinitrate and use of topical nitroglycerin ointment in 11 patients with previous myocardial infarction reduced considerably for at least 4 hours the determinants of myocardial oxygen consumption—systolic blood pressure, left ventricular ejection time, left ventricular size and triple product. The impairment of left ventricular wall motion was also significantly decreased. Both drugs improved the velocity and e

Continued on page A22

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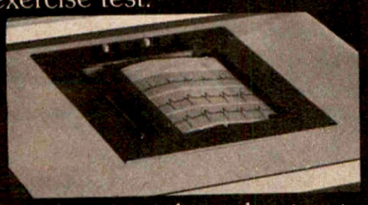
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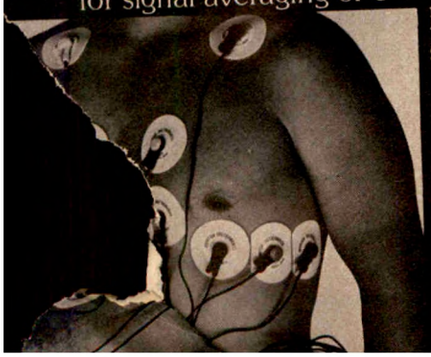
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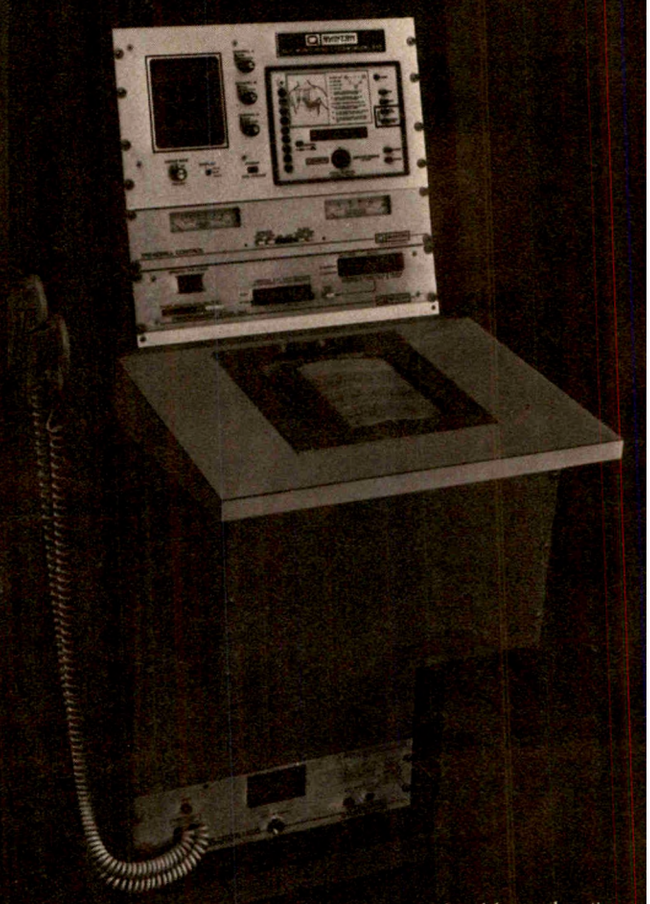
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of contraction of certain areas of the left ventricular wall, particularly segments with moderate impaired function such as hypokinesia and asynchrony. Although orally administered isosorbide dinitrate is probably more convenient for outpatient use, the dose and duration of action of nitroglycerin ointment may be more easily controlled in hospital patients with angina pectoris at rest.

99 **Hemodynamic Effects of Intravenously Administered Quinidine on the Transplanted Human Heart**

JAY W. MASON, ROGER A. WINKLE, NEIL B. INGELS, GEORGE T. DAUGHTERS, DONALD C. HARRISON and EDWARD B. STINSON

Quinidine, 10 mg/kg body weight, infused over a 20 minute period in five heart transplant recipients with an anatomically denervated heart exerted no acute inotropic myocardial effects. Its hemodynamic action was most consistent with peripheral venodilatation. End-diastolic, end-systolic and stroke volumes decreased by an average of 19, 26 and 18 percent, respectively. Cardiac output and mean aortic blood pressure decreased 18 percent and 11 percent, respectively, while the contractile state of the left ventricle was not significantly changed. Although quinidine does not appear to produce myocardial depression directly, it may exert complex effects upon both the cardiac and the peripheral autonomic nervous system, leading to direct peripheral vasomotor changes. Patients with congestive heart failure may be especially susceptible to such unfavorable hemodynamic effects of quinidine.

STUDIES ON HYPERTENSION

105 **Blood Pressure, Renin Activity and Heart Rate Changes During Propranolol Therapy of Hypertension**

ANDREW ZWEIFLER and MURRAY ESLER

Changes in plasma renin, heart rate and blood pressure produced with small doses of propranolol and a dose of 320 mg/day were compared in 24 men with essential hypertension and differing initial levels of renin activity. Although plasma renin decreased significantly in those with normal and high renin levels taking 40 mg/day of propranolol, blood pressure remained unchanged in the normal renin group and only a small decrease in systolic pressure occurred in those with high plasma renin. Patients with low renin levels had no reduction in blood pressure with small doses of propranolol, but responded well to 320 mg/day. These results tend to refute the hypothesis that propranolol decreases blood pressure because it decreases renin activity. Clinically the absence of a heart rate effect in patients with a suboptimal blood pressure response during propranolol therapy indicates inadequate plasma levels of propranolol.

REVIEWS

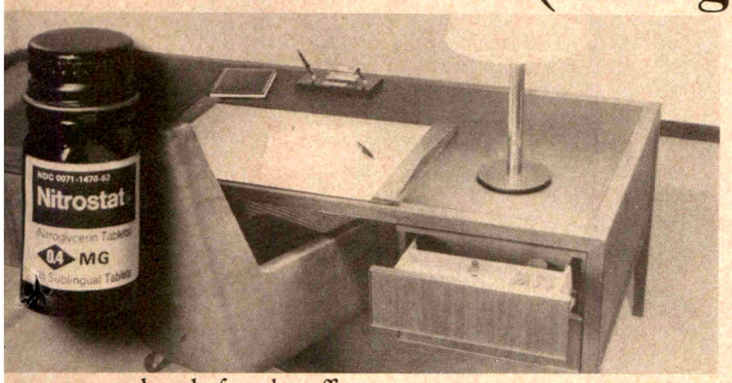
110 **TQ-ST Segment Mapping: Critical Review and Analysis of Current Concepts**

ROGER P. HOLLAND and HAROLD BROOKS

This review critically examines the TQ-ST segment, the historical development of its use, current methods for recording and measuring the deflection, the nomenclature used in its

Continued on page A25

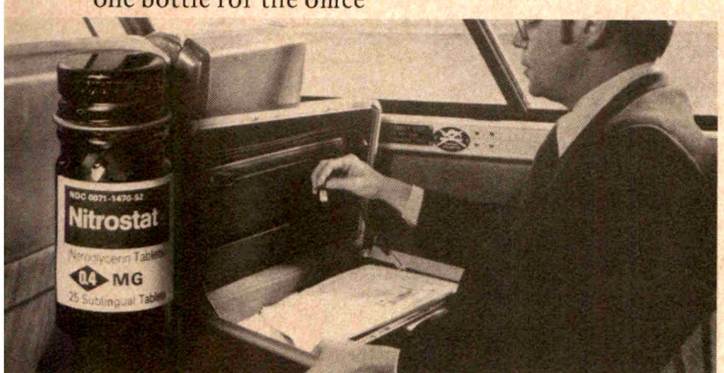
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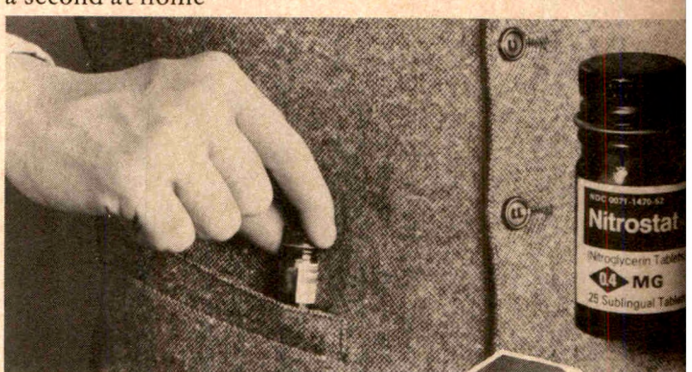
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characterization, its theoretic basis and its modification by changes in ischemic geometry and pharmacologic intervention. The TQ-ST deflection originates primarily but not exclusively as a result of extracellular potassium accumulation in the ischemic area and subsequent transmembrane potential gradient during diastole and systole at the ischemic boundary. Before mapping techniques can be used reliably to quantitate and modify ischemic change, further study of the complex behavior of the TQ-ST segment deflection, particularly in the presence of pharmacologic intervention, is necessary.

CASE REPORTS

130 **Mitral Valve Aneurysm After Infective Endocarditis in the Billowing Mitral Leaflet Syndrome**

WENDY A. POCOCK, JEFFREY B. LAKIER, J. FRANCOIS HITCHCOCK and JOHN B. BARLOW

Infective endocarditis due to a staphylococcal infection produced severe mitral regurgitation associated with a large perforated aneurysm of the anterior mitral valve leaflet in a 34 year old woman previously found to have a billowing mitral leaflet syndrome. After replacement of the mitral valve with a Bjork-Shiley prosthesis 9 years after the infection, the patient remained well. In retrospect, the presence of the presystolic murmur and the angiographic appearance should have led to the preoperative diagnosis of the aneurysm rather than the erroneous impression of marked prolapse of the mitral valve secondary to ruptured chordae tendineae.

133 **Coexisting Right and Left Hypertrophic Subvalvular Stenosis and Fixed Left Ventricular Outflow Obstruction Due to Aortic Valve Stenosis**

ERIC E. HARRISON, SHELDON S. SBAR, HUGH MARTIN and DENNIS F. PUPELLO

Right- and left-sided subvalvular hypertrophic stenosis in this 70 year old woman with aortic valve stenosis developed secondary to left ventricular pressure overload. At cardiac catheterization the pressure gradient across the aortic valve was 120 mm Hg, 90 in the subvalvular area and 15 in the subvalvular area beneath the pulmonary valve. Aortic valve replacement and excision of subaortic hypertrophied muscle were performed.

EDITORIAL

137 **The Disputed S-T Segment Mapping: Is the Technique Ready for Wide Application in Practice?**

BORYS SURAWICZ, MD

SPECIAL DEPARTMENTS

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Ventricular Ectopy in Healthy Subjects—J. P. Liss, Jr. and H. L. Kennedy

Exercise Testing and Coronary Arteriography—J. P. Liss, Jr.

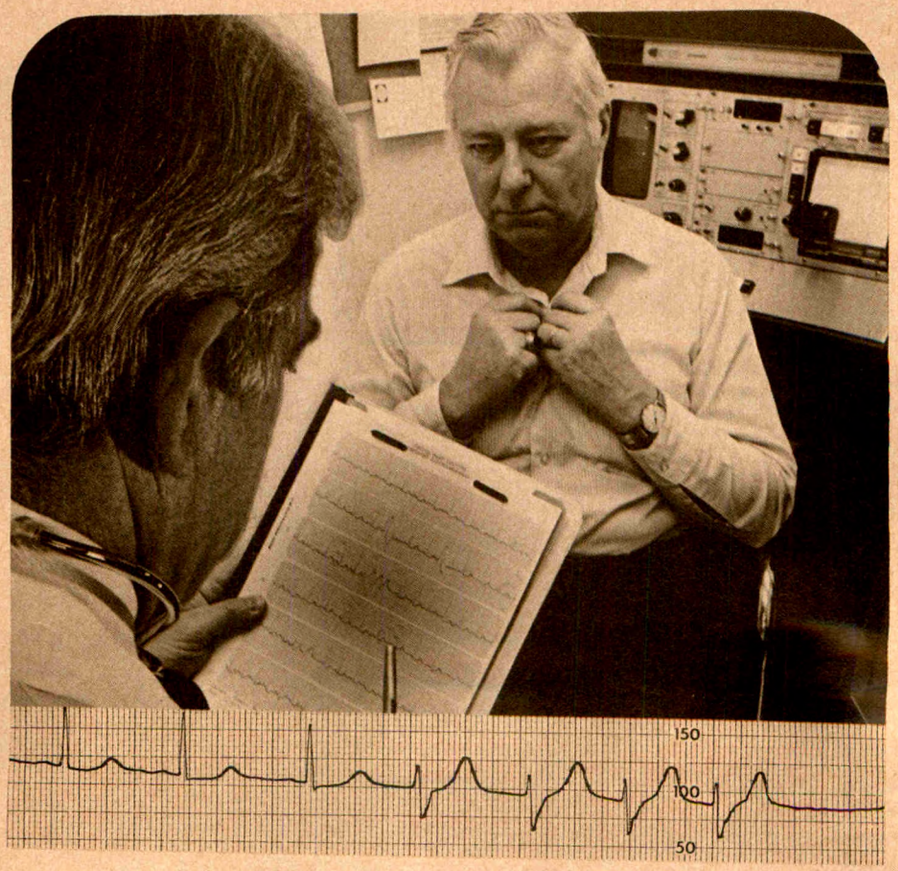
Standardized Regimen for Applying Nitroglycerin Ointment—H. W. Adkison and P. W. Armstrong

144 **American College of Cardiology News**

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Diagnosis: PVC's

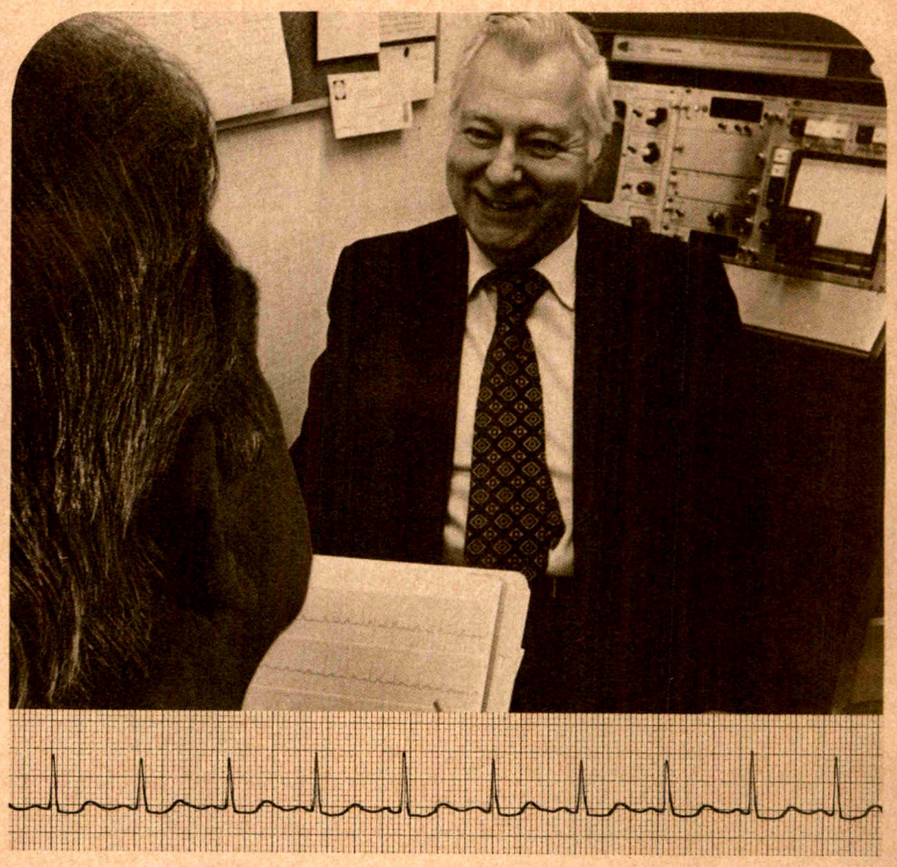
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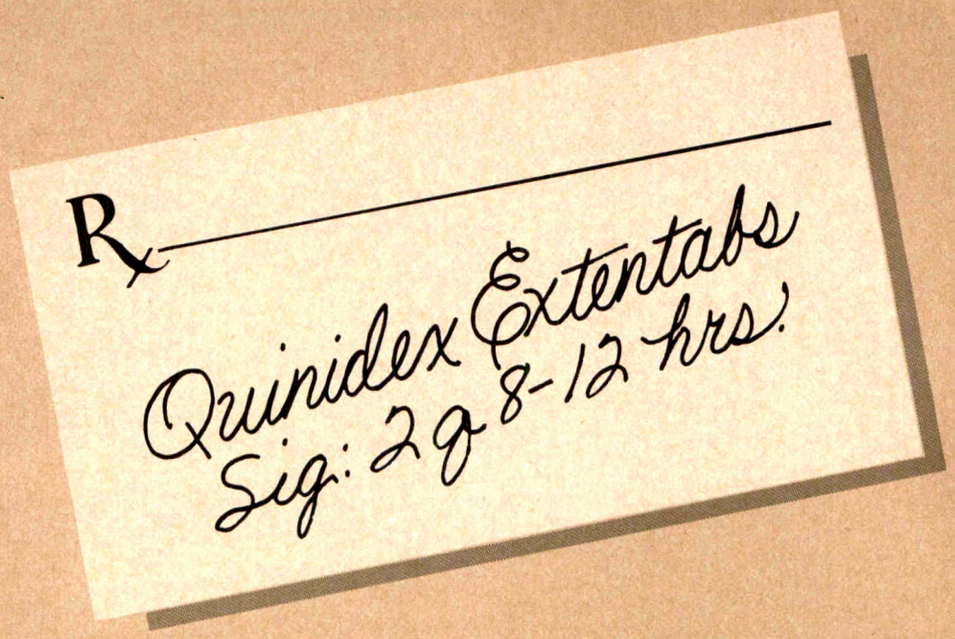
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Quinidex Extentabs are indicated in the treatment of:
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Paroxysmal A-V junctional rhythm.
Atrial flutter.
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Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

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Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

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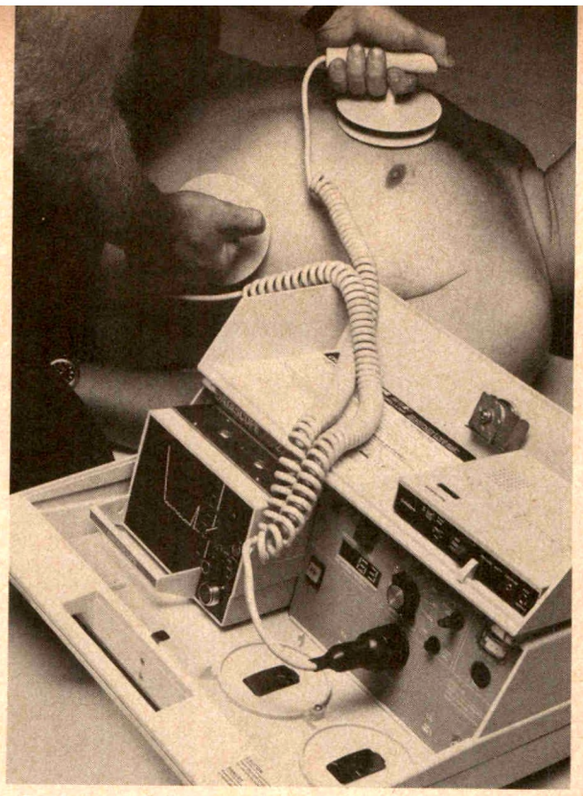
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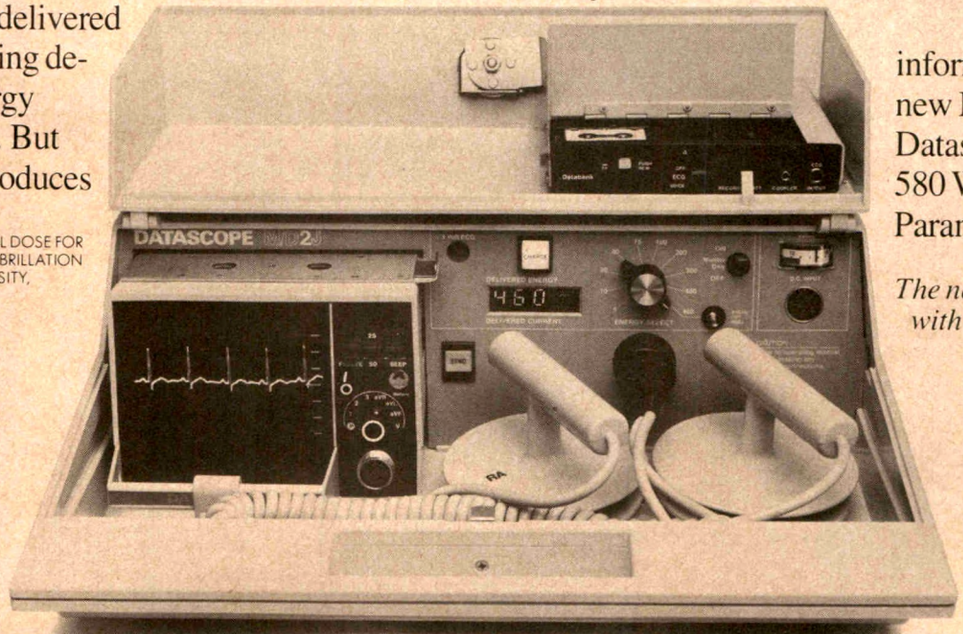
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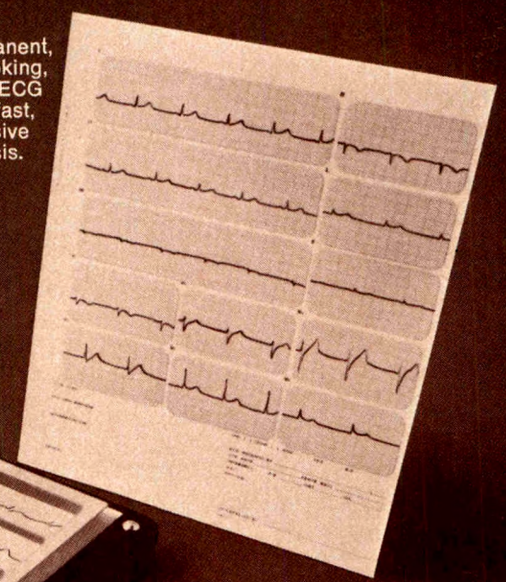
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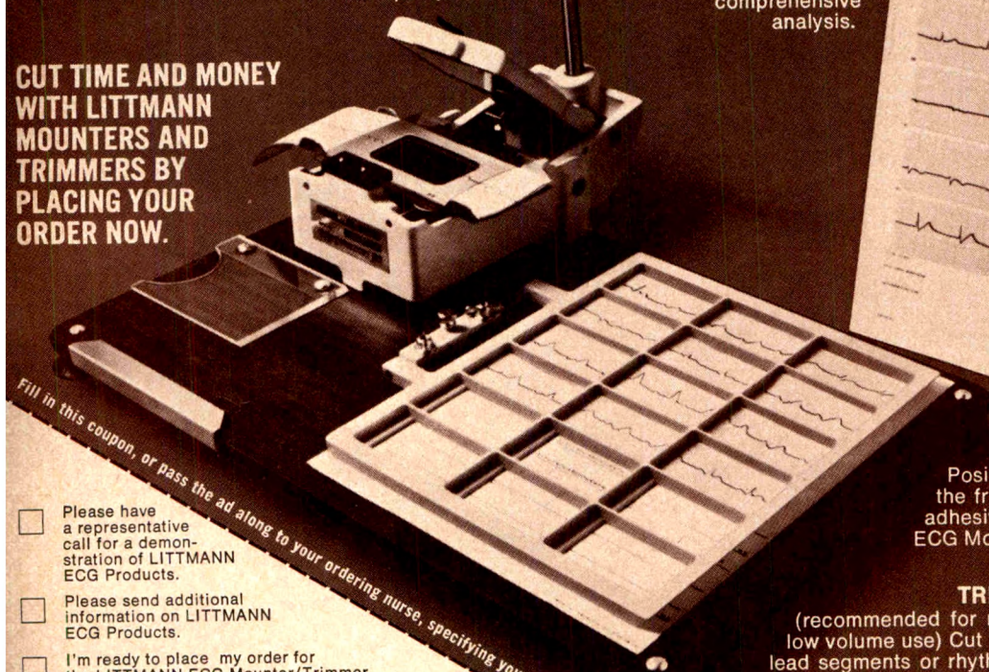
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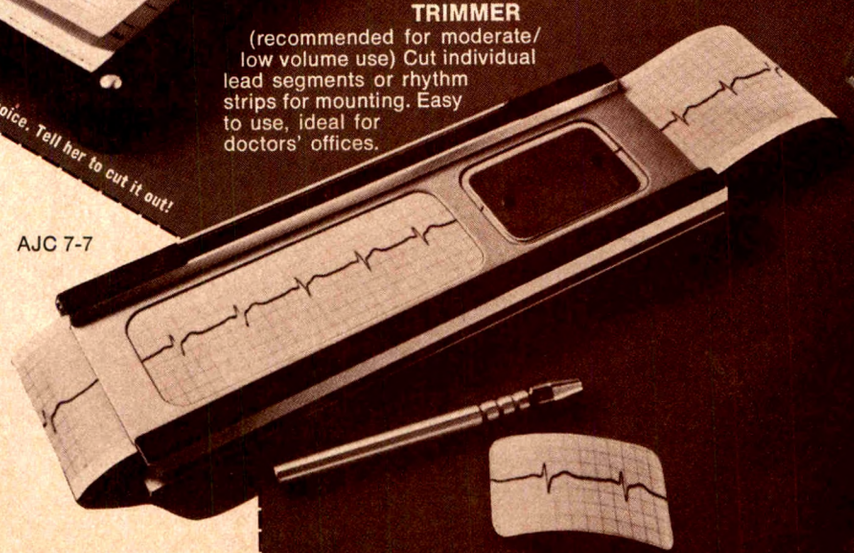
Hold a permanent, professional-looking, 8½ in x 11 in ECG record for fast, comprehensive analysis.





Position individual leads against the frame, press into place against adhesive-backed LITTMANN® Brand ECG Mount. Lift entire alignment frame.

TRIMMER
(recommended for moderate/low volume use) Cut individual lead segments or rhythm strips for mounting. Easy to use, ideal for doctors' offices.



Fill in this coupon, or pass the ad along to your ordering nurse, specifying your choice. Tell her to cut it out!

☐ Please have a representative call for a demonstration of LITTMANN ECG Products.

☐ Please send additional information on LITTMANN ECG Products.

☐ I'm ready to place my order for the LITTMANN ECG Mounter/Trimmer I've indicated below. I understand that this order will be processed by a local surgical supply dealer.

Model No.	Product Information	Regular Price Unit	Special Price Unit	No. of Units Desired
	MOUNTERS			
104	(for lead segments 1⅝ in x 3½ in)	$224.70	$202.23	_____
105	(for lead segments 1½ in x 2½ in)	$224.70	$202.23	_____
	TRIMMERS			
205	(for lead segments 1½ in x 2½ in, 1½ in x 5 in, & 1½ in x 7⅝ in)	$ 45.85	$ 41.27	_____
206	(for lead segments 1⅝ in x 3½ in, 1½ in x 7⅝ in)	$ 45.85	$ 41.27	_____

AJC 7-7

Mail to: 3M Company, Medical Products Division, 3M Center, 223-3S, St. Paul, MN 55101.

Name_____

Hospital/Clinic_____

Address_____

City_____ State_____ Zip_____

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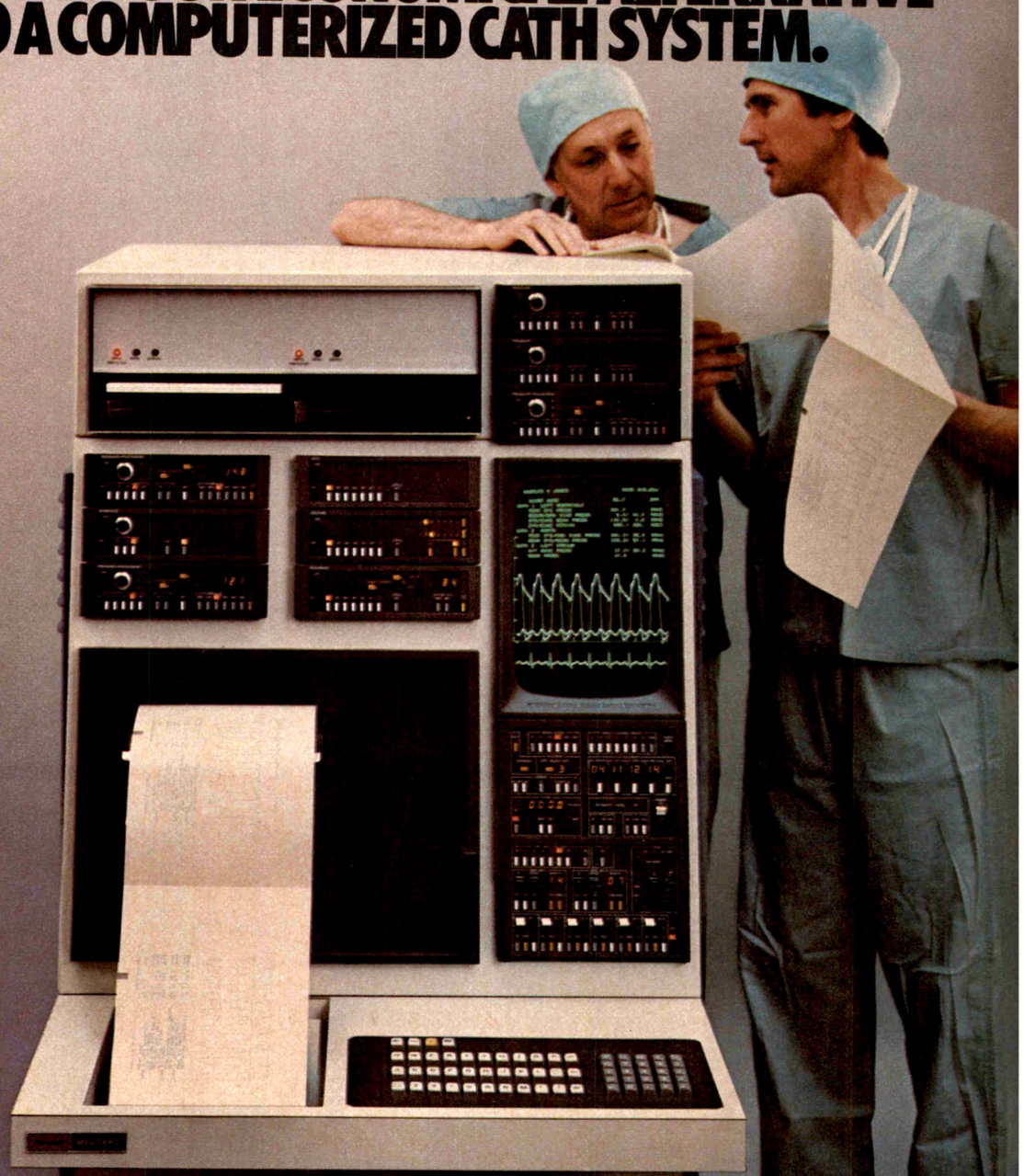
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3M COMPANY

Imagine a compact cardiac cath system that automatically calculates hemodynamic functions. Generates an immediate report from selected data. Lets you program your own cath lab protocols. Manipulates and freezes displayed data for easier analysis Has plug-in signal conditioning for a variety of physiological measurements. Has microprocessor control for simple setup and operation.

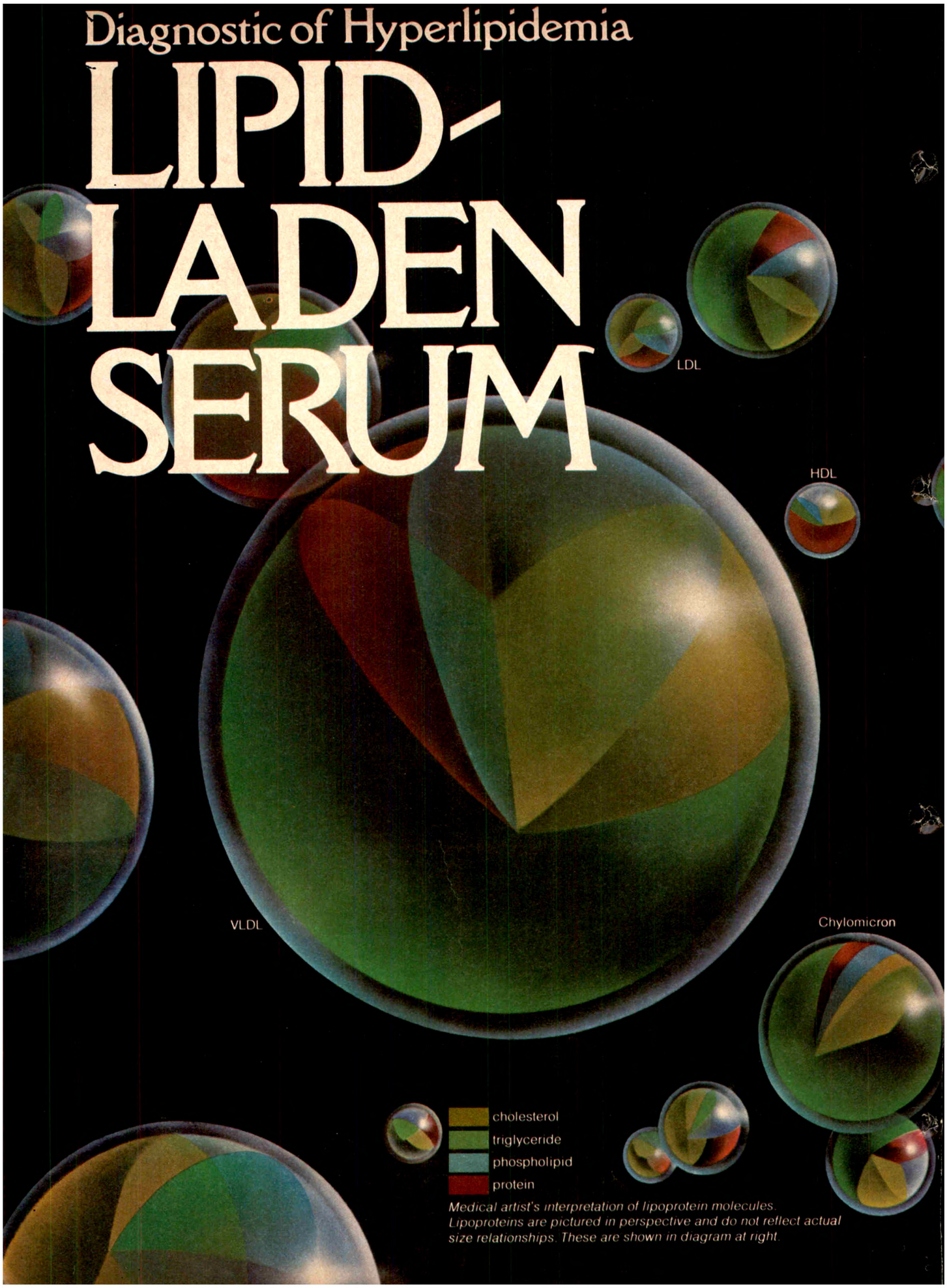
That's big-system convenience and efficiency. But you get it all for a fraction of the cost in the new MEDDARS Series 300. For full details, contact: Stan Edwards, Honeywell Physiological Data Systems, Box 5227, Denver,CO 80217. (303) 771-4700.

MEDDARS. YOUR ECONOMICAL ALTERNATIVE TO A COMPUTERIZED CATH SYSTEM.



WE'LL SHOW YOU A BETTER WAY.

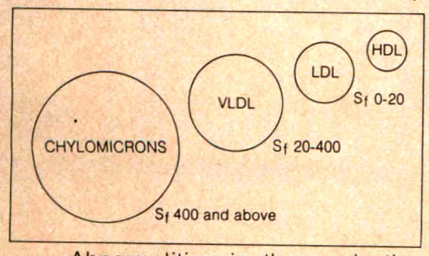
Honeywell


Diagnostic of Hyperlipidemia
LIPID-LADEN SERUM
LDL
HDL
VLDL
Chylomicron
cholesterol
triglyceride
phospholipid
protein
Medical artist's interpretation of lipoprotein molecules. Lipoproteins are pictured in perspective and do not reflect actual size relationships. These are shown in diagram at right.

Lipoproteins: The "cargo" and the "transport vehicle"

Since fats are insoluble in water, they must link up with protein to remain dispersed in the blood. The lipoprotein molecules thus formed allow lipid substances—cholesterol, triglycerides, phospholipids—to travel freely in a soluble form through the bloodstream for use as structural building blocks and sources of energy. The four major classes of lipoprotein, consisting of varying amounts of lipids (the "cargo") and protein (the "transport vehicle") are chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). [See medical artist's interpretation at left.] The relative size of these lipoprotein molecules, based on measurement of flotation rates via ultracentrifugation, is shown below.

SCHEMATIC RELATION OF SIZE TO FLOTATION RATE (S_f)



Abnormalities in the production and/or degradation of these lipoproteins can lead to excessive accumulations of cholesterol and/or triglycerides in the serum. These elevations in serum lipids, in the absence of underlying causative disease, are diagnostic of hyperlipidemia.

Early intervention—a rational approach to the management of hyperlipidemia

Reducing elevated lipid levels is a rational therapeutic goal at any point in the hyperlipidemic process—but is perhaps most logical in the early stage. This is the stage when most patients are asymptomatic, yet routine cholesterol and triglyceride determinations will disclose that nevertheless they are hyperlipidemic.[1]

If persistent, clinically significant lipid elevations are demonstrated—and underlying disease states are ruled out through history, physical examination, and appropriate laboratory tests—a diagnosis of primary hyperlipidemia is confirmed.

Dietary modification directed at correcting the specific lipid abnormality should be instituted as the first therapeutic step, but it often fails to lower the lipids sufficiently.

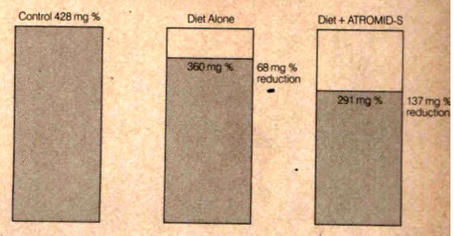
This is the best time to add ATROMID-S, an antilipidemic agent, to the regimen. Early, effective, and continuous lipid lowering is important in the successful management of hyperlipidemia.

When diet alone is not enough, Atromid-S can further reduce elevated serum lipids

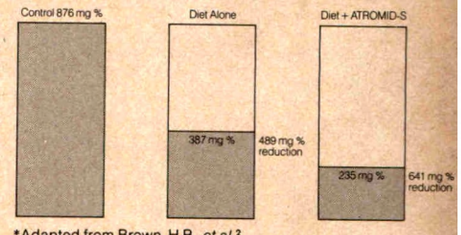
As an adjunct to diet and other measures, ATROMID-S depresses levels of both the very low density lipoproteins (S_f 20-400) and the low density lipoproteins (S_f 0-20), with an apparently greater effect on the former. The result of these actions is a reduction in elevated serum cholesterol (particularly the cholesterol carried by LDL) and/or triglycerides.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

ATROMID-S Lowers Cholesterol Significantly Better Than Diet Alone
Results in 7 patients with hypercholesterolemia
Mean Difference mg %*



ATROMIDS-S Lowers Triglycerides Significantly Better Than Diet Alone
Results in 7 patients with hypertriglyceridemia
Mean Difference mg %*



*Adapted from Brown, H.B., *et al*.[2]

Continuous therapy and constant dosage essential to long-term control

Lipid lowering is sustained as long as ATROMID-S treatment is uninterrupted. However, if the drug is stopped, lipid levels may return to or above pretreatment levels.

ATROMID-S is effective in a simple, well-accepted regimen. Initial *and* maintenance dosage is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

As an adjunct to diet

Atromid-S®

Brand of

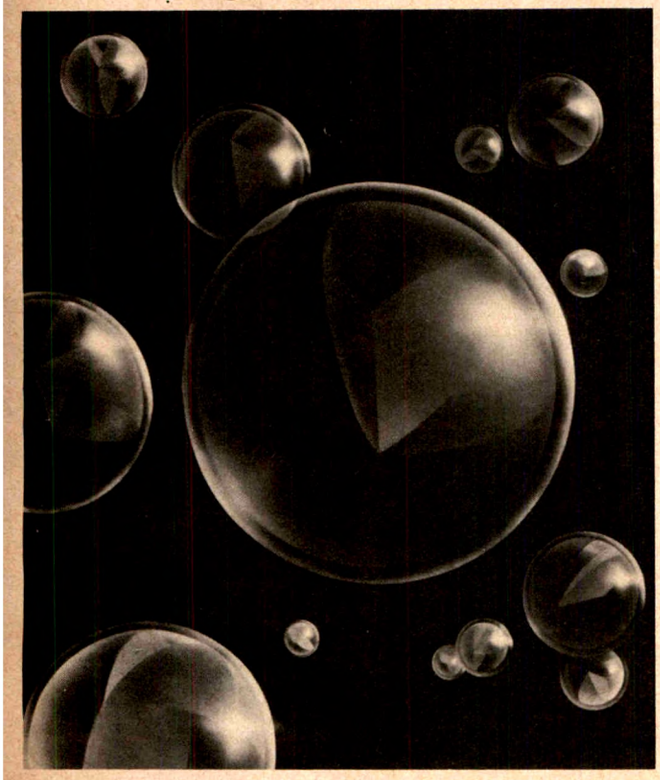
clofibrate

Helps reduce elevated serum levels of cholesterol and/or triglycerides

See last page of this advertisement for prescribing information.

Atromid-S® (clofibrate)

Helps reduce elevated serum levels of cholesterol and/or triglycerides



BRIEF SUMMARY
(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

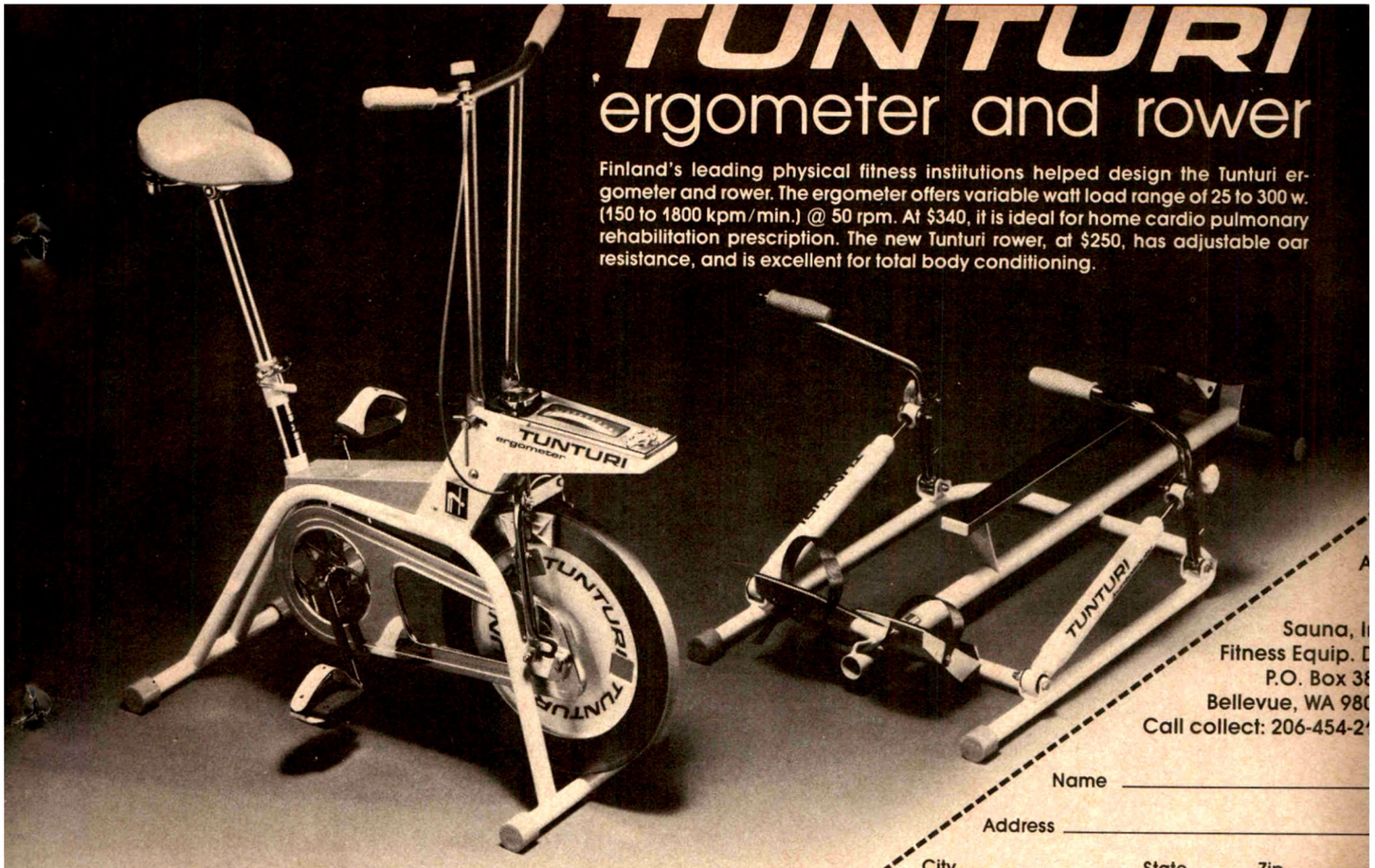
References: 1. Scheig, R.: Conn. Med. *39*:71 (Feb.) 1975. **2.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. *17*:171 (Feb.) 1975.

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TUNTURI
ergometer and rower

Finland's leading physical fitness institutions helped design the Tunturi ergometer and rower. The ergometer offers variable watt load range of 25 to 300 w. (150 to 1800 kpm/min.) @ 50 rpm. At $340, it is ideal for home cardio pulmonary rehabilitation prescription. The new Tunturi rower, at $250, has adjustable oar resistance, and is excellent for total body conditioning.



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Ambulatory Blood Pressure Recorder



Light, compact one-piece unit weighs only 25 ounces.

The Remler patented Ambulatory Blood Pressure Recorder has been in use for more than ten years by leading physicians and research institutions throughout the world. It is a proven, easy-to-use system that relieves the doctor of the time-consuming traditional auscultatory procedure.

Now, by miniaturizing circuits and components, we have produced a smaller and easier to wear *single-unit* version.

This Model M-2000 records blood pressures during the wearer's working or leisure day. Wearing this unobtrusive, lightweight device on a belt, any patient can easily record blood pressure data onto the micro-cassette as many as fifty times daily. This method *totally eliminates bias,* and the pressor effect of an observer's presence.

The Remler system is especially useful in determining the efficacy of medication in the treatment of hypertension.

AJC-7/77

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Please send me complete details on the new
Remler M-2000 Ambulatory Blood Pressure Recorder.

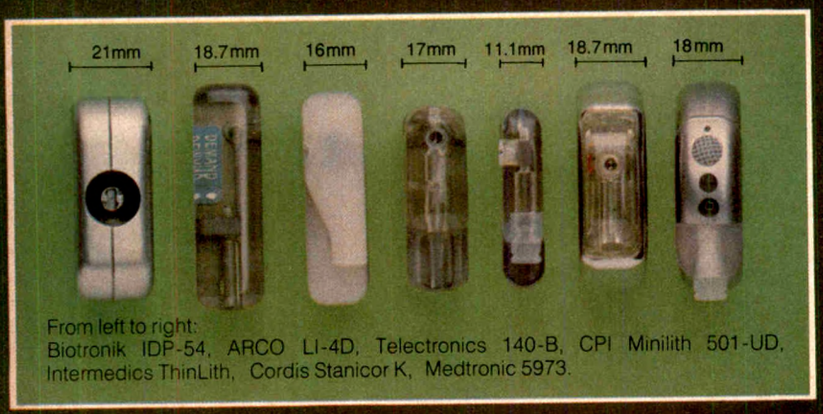
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Address _____

City/State/Zip _____

ThinLith™

Today's thinnest lithium pacemaker.



From left to right:
Biotronik IDP-54, ARCO LI-4D, Telectronics 140-B, CPI Minilith 501-UD, Intermedics ThinLith, Cordis Stanicor K, Medtronic 5973.

Part of a total superior system from Intermedics, Inc.

Intermedics now offers the *thinnest* lithium cardiac pulse generator available in the world today — the ThinLith. The unipolar ThinLith,



which measures only 11.1mm in thickness, virtually eliminates the skin bulge common with thicker pulse generators, adds to patient comfort and greatly reduces skin pressure necrosis. In addition, the ThinLith's light weight and smoothly rounded corners reduce the chance of migration within the body.

The ThinLith employs the same dependable C-MOS circuitry which has proven successful in other Intermedics pulse generators. This double ion diffusion C-MOS circuitry provides optimum sensing and stimulation performance, even at low voltage levels. To aid in the creation of the ThinLith, we have greatly reduced the number of components and miniaturized the electronics by using a hybrid circuit which employs advanced technology in microelectronics.

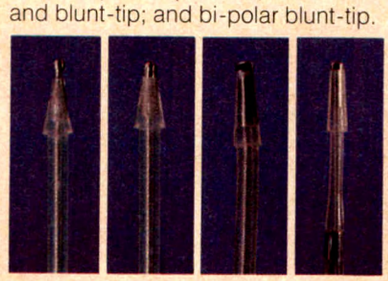
As a power source, Intermedics' engineers chose the highly reliable Catalyst Research, single cell, lithium-iodine battery, proven in testing and in human use for five years. This power source has a theoretical longevity of ten years and is backed by Intermedics with a 72 month replacement credit agreement.

After assembly and testing, the circuitry and power source are hermetically sealed in electromagnetic interference resistant, 316L stainless steel and sterilized for implant. The ThinLith, as are all Intermedics pulse generators, is designed to accept all of the more commonly used leads without need for an adapter.

The predecessors to the Intermedics ThinLith are the unipolar C-MOS I mercury-zinc pulse generator and the C-MOS I Lithium, and the InterLith™ generators in unipolar and bipolar models. These have been the choice of pacemaker implants around the world.

Life-Prolonging Leads

As part of their life support system, Intermedics manufactures a quality line of high density, platinum-tipped leads which provide low pacing and sensing thresholds, thereby increasing the longevity of the pulse generator. Materials for lead manufacture were carefully selected for their chemical and functional compatibility as well as their strength and flexibility. Closed coil construction resists dislodgement and prevents lead fractures and provides lead flexibility so important to the physician. Intermedics' leads are available in a variety of tip configurations: unipolar spherical, conical and blunt-tip; and bi-polar blunt-tip.



Trans-Telephonic Monitoring Systems At No Additional Charge

Intermedics is the only pacemaker manufacturer in the market today which provides the patient with a trans-telephonic monitoring service — Trace-A-Pace™ *— absolutely free of charge to the patient, physician, or heatlh carrier. At the request of the physician, the patient receives a light-weight and easy-to-use (requires no electrode wires) transmitter. Then, at intervals determined by the physician, the patient simply dials our toll-free number and has a rhythm strip and digital interval rate count recorded. In all cases, the physician receives a full report and copy of the rhythm strip by mail. However, should an irregularity be observed, the



physician is notified immediately by telephone. This service greatly reduces the time required for patient follow-up and increases the patient's confidence and mobility.

24-Hour Service

All Intermedics' representatives are on call 24 hours a day. When necessary, they can have an Intermedics implantable device in your hands shortly after you call.

For the location of your nearest Intermedics representative, or for additional information about our products, call toll-free 1-800-231-2330. In Texas, call collect 1-713-233-8611.

Intermedics Inc.
P.O. Box 617 • Freeport, Texas 77541

For further information concerning Intermedics or any of its products, clip and return this coupon.

Name _____

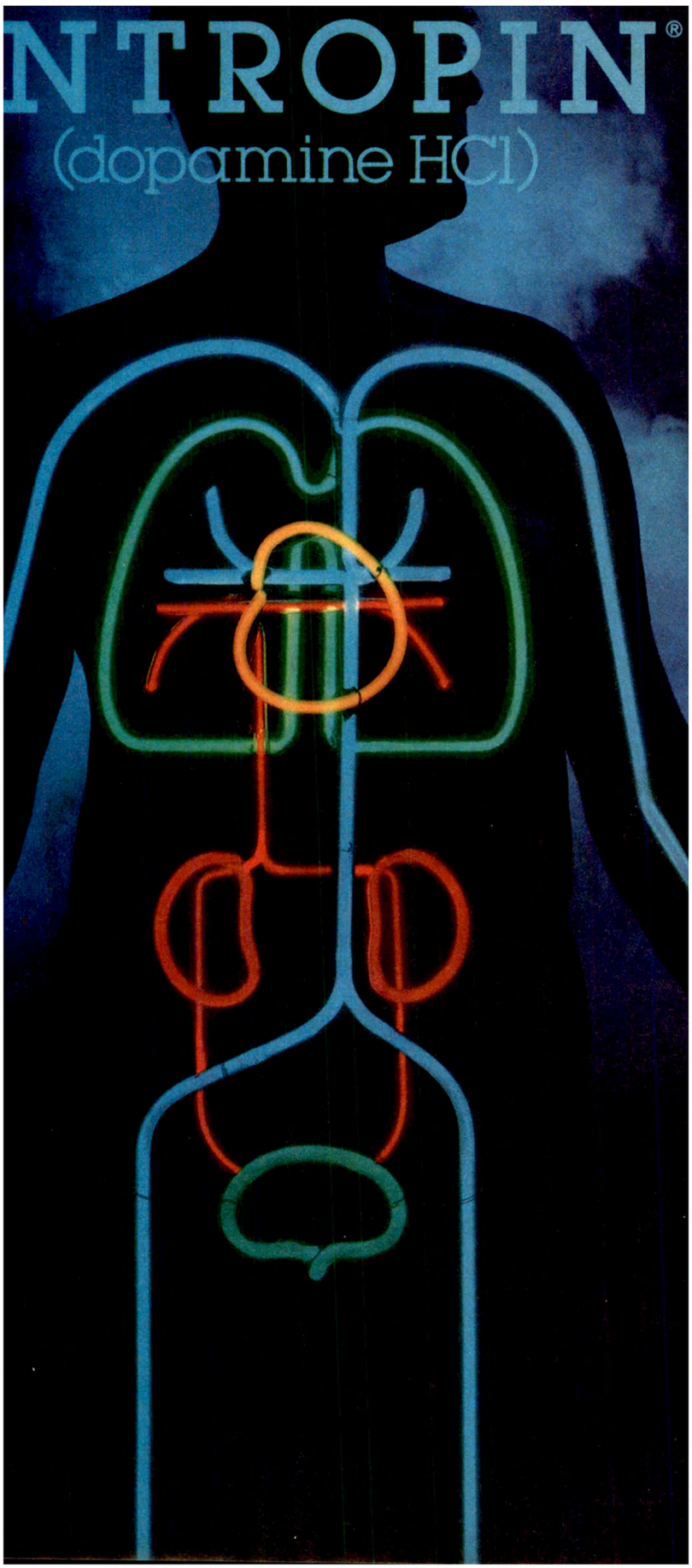
Address _____

City _____ State ____ Zip ____

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*Trace-A-Pace equipment is manufactured by Instromedix, Inc. Beaverton, Oregon.

ThinLith™, InterLith™ and Trace-A-Pace™ are registered trademarks of Intermedics, Inc.


NTROPIN®
(dopamine HCl)

In the shock syndrome:

Selectively redirects blood to vital organs

Increases vital organ perfusion

In the shock syndrome, perfusion pressure usually does not meet the metabolic needs of the vital organs. When volume replacement fails to reverse this process, additional therapy must be initiated to increase cardiac output and blood pressure and to increase blood flow to vital organs.

Intropin (dopamine HCl) is the only drug that both increases cardiac output and blood pressure while specifically redirecting the blood flow.

Maintains kidney function

The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

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Mount Prospect, Illinois 60056
A Subsidiary of American Hospital Supply Corporation

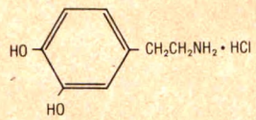
INTROPIN® (dopamine HCl)

(See last page of this advertisement for full prescribing information.)

INTROPIN® (dopamine HCl)

5 ml. AMPUL/FOR I.V. INJECTION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally-occurring biochemical catecholamine precursor of norepinephrine. The chemical structure is:



$C_8H_{11}NO_2 \cdot HCl$ Mol. Wt. 189.65

Dopamine hydrochloride is a white, odorless crystalline powder, freely soluble in water and soluble in alcohol. It is sensitive to light, alkalis, iron salts and oxidizing agents.

Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs—Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output—Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension—Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy—Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children—The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia—Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure—If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation—INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease—Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT—Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics—Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required—Close monitoring of the following indices—urine flow, cardiac output and blood pressure—during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution—Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration—INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized..

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

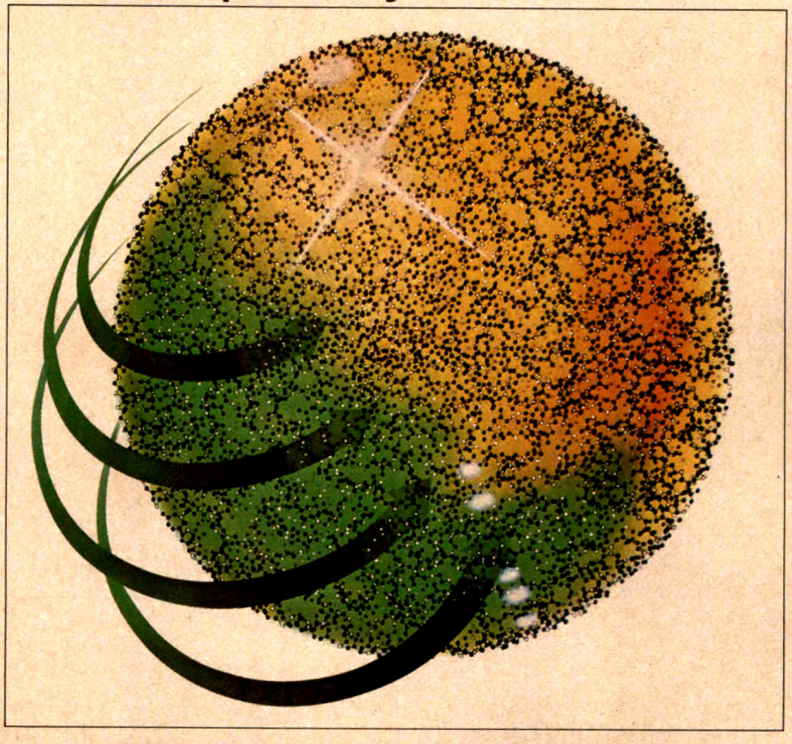
ARNAR-STONE LABORATORIES, INC.
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A Subsidiary of American Hospital Supply Corporation

Upjohn

introduces

new Colestid®

colestipol hydrochloride



Adjunctive to diet

lowers plasma cholesterol through nonsystemic action

A43

Upjohn

new Colestid®

colestipol hydrochloride

Adjunctive to diet lowers serum cholesterol through a nonsystemic action

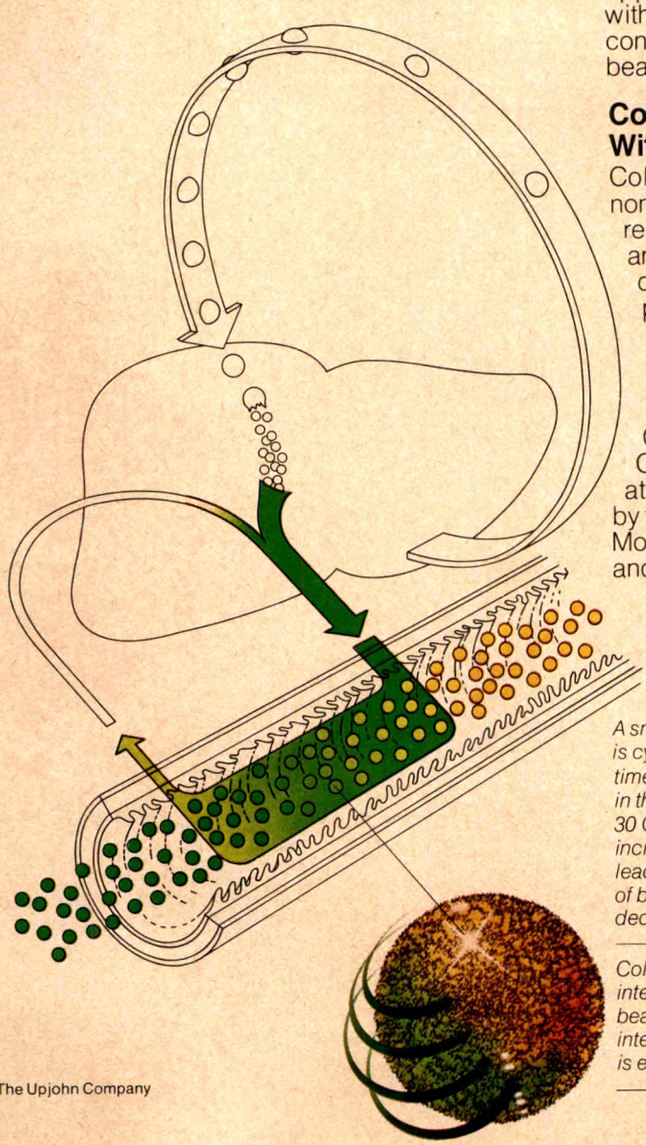
- for primary hypercholesterolemia
- effective long-term adjunct to diet
- nonsystemic mode of action
- offers convenient b.i.d. dosage

Colestid is a high-molecular-weight, anion-exchange copolymer. It consists of virtually insoluble macromolecular beads, each containing approximately 10^{15} potential bile-acid-binding sites within its mesh structure. The average 5 Gm dose contains an estimated 1,250,000 macromolecular beads.

Colestid Acts Only Within the Lumen of the GI Tract

Colestid, a bile sequestrant, is virtually nonabsorbed. Most bile acids are normally reabsorbed; however, the partial removal of a small amount of bile acids from the enterohepatic circulation by Colestid increases hepatic production of bile acids from cholesterol. This results in a decrease in the cholesterol-rich, low-density lipoproteins and thus a decrease in serum cholesterol.

The most common adverse reactions to Colestid are confined to the gastrointestinal tract. Constipation is the major single complaint, and at times is severe and occasionally accompanied by fecal impaction. Hemorrhoids may be aggravated. Most instances of constipation are mild, transient, and controlled with standard treatment.



A small pool of bile acids, about 2 to 4 Gm, is cycled through the intestine several times daily, and only about 0.6 Gm is lost in the feces. With Colestid therapy (15 to 30 Gm/day), the bile salt excretion is increased about 2 to 2½ times. This leads to increased hepatic production of bile acids from cholesterol, thereby decreasing serum cholesterol levels.

Colestid acts within the gastrointestinal tract. Its macromolecular beads bind bile acids in the intestine and form a complex that is excreted in the feces.

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Scope of Colestid Clinical Studies

One hundred and forty-four investigators and over 2,500 patients treated with Colestid (colestipol hydrochloride) participated in clinical trials of this new bile-sequestering agent. Thirty clinical studies helped to determine the efficacy, safety, and tolerance of Colestid in lowering serum cholesterol.

Colestid Therapy Guidelines

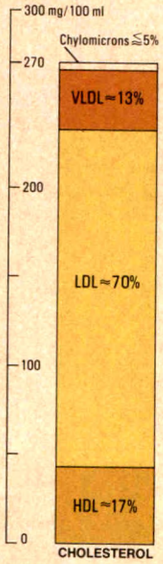
Colestid is indicated as adjunctive therapy to diet in the management of patients with elevated serum cholesterol due to primary hypercholesterolemia (elevated low-density lipoproteins).

The beta-lipoprotein (or low-density lipoprotein) transports most of the serum cholesterol, and it is believed that the fall in serum cholesterol with Colestid therapy is secondary to an increased clearance of the cholesterol-rich, low-density lipoprotein.

The reduction of serum cholesterol levels is usually evident within one month. When Colestid is discontinued, cholesterol levels usually return to baseline levels within one month.

Colestid has been shown to have no effect on, or to increase, triglyceride levels. Failure of cholesterol to fall or a significant rise in the triglyceride level should be considered as indication to discontinue Colestid.

Approximate contribution of the four lipoproteins to total serum cholesterol in a normal subject, fasting state.



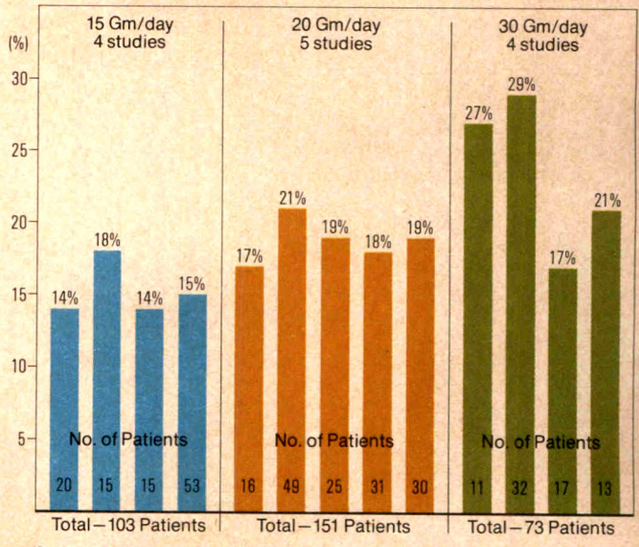
It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Investigations now in progress may yield an answer to this question.

Colestid Offers b.i.d. Convenience

Colestid 10 Gm twice a day is usually effective and avoids the obstacle of midday dosage. In general, however, Colestid dosage may be adjusted to meet the cholesterol-lowering requirements of the individual patient. For adults, the recommended dosage range is 15 to 30 Gm per day, divided into two, three, or four doses. To avoid accidental inhalation or esophageal distress, Colestid should not be taken in its dry form.

Measure of Colestid Efficacy

Average Cholesterol Reduction at 15, 20, and 30 Gm daily



Colestid is recommended in doses of 15 to 30 Gm per day, administered in divided doses, two, three, or four times daily.

Easy and Versatile Administration



The small particle size and neutral taste of Colestid (colestipol hydrochloride) make it a readily acceptable adjunct to your patient's diet. For example, it may be taken conveniently with orange juice in the morning and with applesauce at night. Colestid mixes easily with almost any liquid or pulpy fruit (such as milk, water, fruit juices, carbonated beverages, pineapple, applesauce, cereals, and soups).

Colestid is available in measured-dose packets of 5 Gm (30 to a carton) or in bottles of 500 Gm (with calibrated measuring spoon).

Drug Interactions

Patients should take other drugs at least one hour before or four hours after Colestid to minimize possible interference with their absorption.

Discontinuing Colestid could pose a hazard to health if a potentially toxic drug that is significantly bound to Colestid has been titrated to a maintenance level during Colestid therapy. Particular caution should be observed in digitalized patients, since there are conflicting results for the effect of Colestid on the absorption of digoxin and digitoxin.

For a summary of prescribing information, please see last page of this advertisement.▶

Upjohn

new Colestid®
colestipol hydrochloride

Lowers plasma cholesterol through a nonsystemic action adjunctive to diet

INDICATIONS AND USAGE Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long-term use.

Colestid (colestipol hydrochloride) is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low-density lipoproteins). It has been shown that Colestid has no effect on, or may increase, triglyceride levels.

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on morbidity or mortality due to atherosclerosis, including coronary heart disease. Investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS Colestid (colestipol hydrochloride) is contraindicated in individuals with hypersensitivity to any of its components.

WARNINGS TO AVOID ACCIDENTAL INHALATION OR ESOPHAGEAL DISTRESS, COLESTID SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX COLESTID WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

PRECAUTIONS Before therapy with Colestid, a vigorous attempt should be made to control serum cholesterol with diet and weight reduction; any underlying disorder should be treated.

Colestid may interfere with normal absorption and fat, vitamins A, D, and K. Supplemental vitamins A and D should be considered.

Colestid may be associated with hypoprothrombinemia from vitamin K deficiency and can be prevented by administration of vitamin K1.

Serum cholesterol and triglyceride levels should be monitored. Colestid may raise the serum triglycerides in long-term use and, in some patients, the cholesterol levels return to baseline or rise above baseline.

Colestid may produce or severely worsen preexisting constipation. Dosage should be decreased in these patients, since impaction may occur. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with Colestid may aggravate hemorrhoids.

Use in Pregnancy and Childhood The use of Colestid in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. The safe use of Colestid resin by pregnant women has not been established. Safety and effectiveness in children have not been established.

DRUG INTERACTIONS Colestid may have a strong affinity for anions other than the bile acids. Colestid may delay or reduce the absorption of concomitant oral medication. The interval between the administration of Colestid and any other medication should be as long as possible. Patients should take other drugs at least one hour before or four hours after Colestid.

In vitro Colestid binds a number of drugs. *In vivo* studies disclosed significant effects on drug availability for L-thyroxin and aspirin, and possibly for warfarin and nicotinic acid. Decreased serum tetracycline levels were observed in a clinical study.

In preliminary studies, drug availability did not appear to be significantly altered for phenobarbital, cortisone acetate, chlorpromazine, sulfadiazine, clofibrate, and hydrochlorothiazide. Particular caution should be observed with digitalis preparations, since there are conflicting results for the effect of Colestid on the availability of digoxin and digitoxin. Discontinuing Colestid could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking Colestid.

ADVERSE REACTIONS

1. Gastrointestinal The most common adverse reactions are gastrointestinal. Constipation, one patient in 10, is the major single complaint and at times is severe and occasionally accompanied by fecal impaction. Hemorrhoids may be aggravated. Some patients require decreased dosage or discontinuation of therapy. About one in 30 to one in 100 patients reported abdominal discomfort (abdominal pain and distention), belching, flatulence, nausea, vomiting, and diarrhea. Peptic ulceration, gastrointestinal irritation and bleeding, cholecystitis, and cholelithiasis have been reported by fewer than one in 500 patients and are not necessarily drug related.

2. Hypersensitivity Urticaria and dermatitis were noted in fewer than one in 1,000 patients. Asthma and wheezing were not reported in the Colestid studies but have been noted during treatment with other cholesterol-lowering agents.

3. Musculoskeletal Muscle and joint pains and arthritis have had a reported incidence of less than one in 1,000 patients.

4. Neurologic Headache and dizziness were noted in about one in 300 patients; anxiety, vertigo, and drowsiness were reported in fewer than one in 1,000.

5. Miscellaneous Anorexia, fatigue, weakness, and shortness of breath have been seen in 1 to 3 patients in 1,000. Transient and modest elevations of serum glutamic oxaloacetic transaminase and of alkaline phosphatase were observed in various patients treated with Colestid. Some patients had increased serum phosphorus and chloride with decreased sodium and potassium.

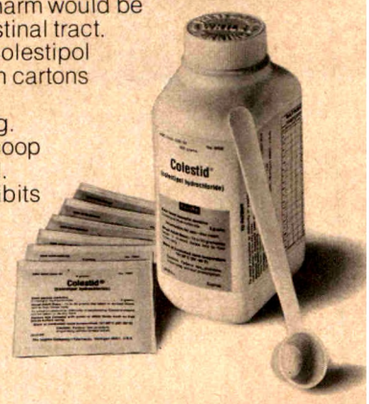
OVERDOSE Overdosage of Colestid (colestipol hydrochloride) has not been reported. Should overdosage occur, however, the chief potential harm would be obstruction of the gastrointestinal tract.

HOW SUPPLIED Colestid (colestipol hydrochloride) is available in cartons of 30 packets and in bottles containing 500 grams of drug. Each packet or each level scoop supplies 5 grams of Colestid.

Caution: Federal law prohibits dispensing without prescription.

For additional information, see your Upjohn representative or consult package circular.

MED-1



Upjohn The Upjohn Company, Kalamazoo, Michigan 49001, U.S.A.

J-4815-6

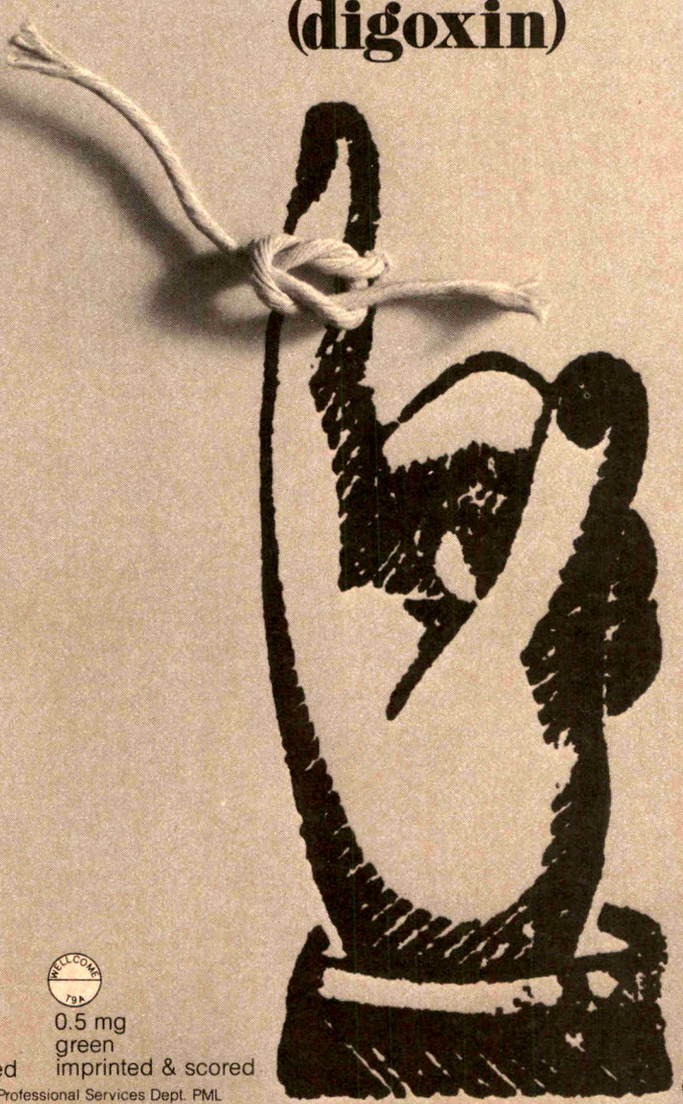
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JULY 1977

The American Journal of CARDIOLOGY®

VOLUME 40

NUMBER 1

CLINICAL STUDIES

Technetium-99m Pyrophosphate Myocardial Uptake in Patients With Stable Angina Pectoris

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Stanford, California

99m-technetium (Tc) pyrophosphate myocardial scintigrams of 55 patients with stable angina pectoris were compared with those of 13 normal subjects. The mean scintigraphic score, obtained by averaging the blinded interpretations of four readers scoring on an integral scale from 0 to 4, was significantly higher for the patients with angina than for the control subjects (1.36 compared with 0.48, $P < 0.001$). Among the patients with angina, those who had a prior myocardial infarction had a higher mean scintigraphic grade than those without a previous infarction (1.73 versus 1.15, $P < 0.005$), and the mean grade in both groups was higher than that of control subjects ($P < 0.001$). Radionuclide uptake was predominantly diffuse in the patients with angina pectoris (70 percent), although in those with greater uptake accumulation tended to be localized. Three of the 68 subjects had high levels of radionuclide uptake but no clinical evidence of acute myocardial injury. This study demonstrates that excess myocardial accumulation of 99m-Tc pyrophosphate can occur in patients with stable angina pectoris.

Pyrophosphate labeled with technetium-99m (99m-Tc pyrophosphate) accumulates in infarcted cardiac muscle.[1,2] Myocardial pyrophosphate uptake has also been described in patients with unstable angina pectoris.[2,3] Although the specific mechanism for pyrophosphate uptake by the myocardium remains unclear, accumulation does occur in myocytes with increased calcium content[4]; both ischemia[5,6] and necrosis increase myocyte calcium levels.[7,8]

This study documents excess myocardial scintigraphic uptake of 99m-Tc pyrophosphate in patients with stable angina pectoris. In myocardial scintigraphy with 99m-Tc pyrophosphate, as in other types of scintigraphy, a spectrum of radionuclide uptake is observed. For this reason a strict dichotomous separation of scintigrams into "normal" and "abnormal" categories can be difficult in individual cases and may result in a loss of useful information. In this study each scintigram was assigned a grade, derived from four observers' interpretations, to allow a comparison of scintigraphic findings in patients with angina pectoris and subjects without cardiac disease.

From the Divisions of Cardiology and Nuclear Medicine and the Department of Cardiovascular Surgery, Stanford University School of Medicine, Stanford, California. This work was supported in part by a gift from the Henry J. Kaiser Family Foundation, Palo Alto, California, and by Grant HL-5866 and Program Project Grant 1-P01-HL-15833 from the National Institutes of Health, Bethesda, Maryland. Dr. Stinson was supported in part by an established Investigatorship of the American Heart Association, Dallas, Texas. Manuscript received August 5, 1976; revised manuscript received December 2, 1976, accepted January 12, 1977.

Address for reprints: Jay W. Mason, MD, Stanford University School of Medicine, Cardiology Division, Stanford, California 94305.

TABLE I

Patients With Stable Angina Pectoris Undergoing Myocardial Scintigraphy

	no. of Patients
Total	55
Female	13
Male	42
Previous myocardial infarction	19
No prior myocardial infarction	36
Single vessel disease	8 (2)
Two vessel disease	11 (5)
Three vessel disease	23 (6)
More than three vessel disease†	13 (7)

Figures in parentheses indicate the number of patients in each category with previous myocardial infarction, as determined with electrocardiographic criteria.
† See text.

Materials and Methods

Subjects: Fifty-five patients with stable angina pectoris were studied 1 to 3 days before electively scheduled coronary arterial bypass grafting. Informed consent was obtained. Only patients with clinically stable angina pectoris were accepted for investigation. In these patients the chest pain was predominantly exertional and relieved by nitroglycerin. A data profile of the 55 patients is presented in Table I. Seventy-six percent were men and 65 percent had significant coronary artery disease in more than two vessels. Twenty patients (36 percent) had had a previous myocardial infarction, in no case within 6 months of the study. All 55 patients underwent coronary arteriography within 6 weeks of electively scheduled bypass grafting.

In addition to the 55 patients with angina, 13 subjects without evidence of cardiac disease, renal failure or cachexia

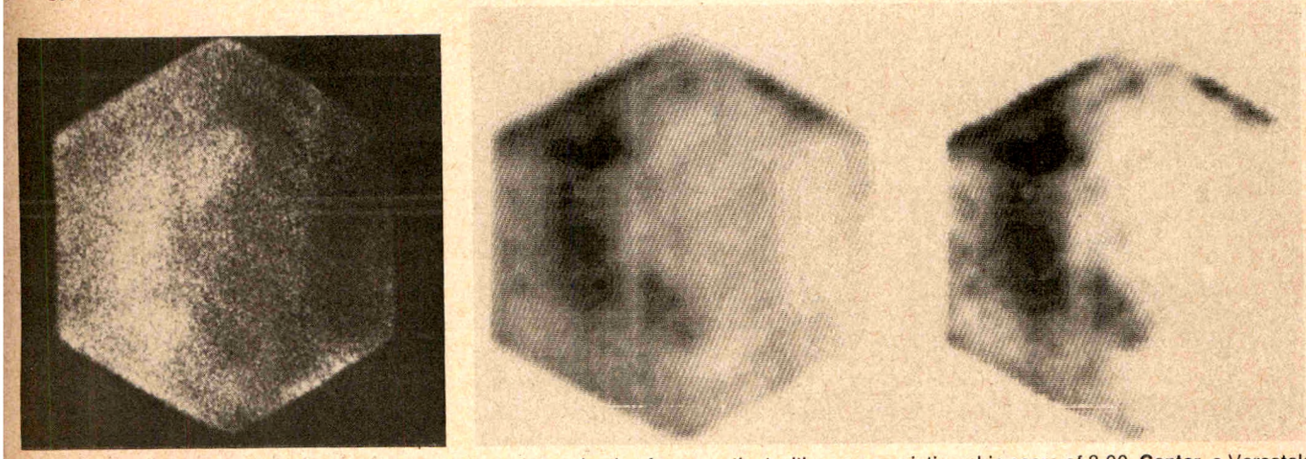


FIGURE 1. Left, a direct Polaroid photograph of an anterior projection from a patient with a mean scintigraphic score of 3.00. **Center,** a Versatek pseudogrey-shade hard copy printout of the same data in which the scale has been set to cover the actual count range. **Right,** a contrast-enhanced Versatek printout (see text).

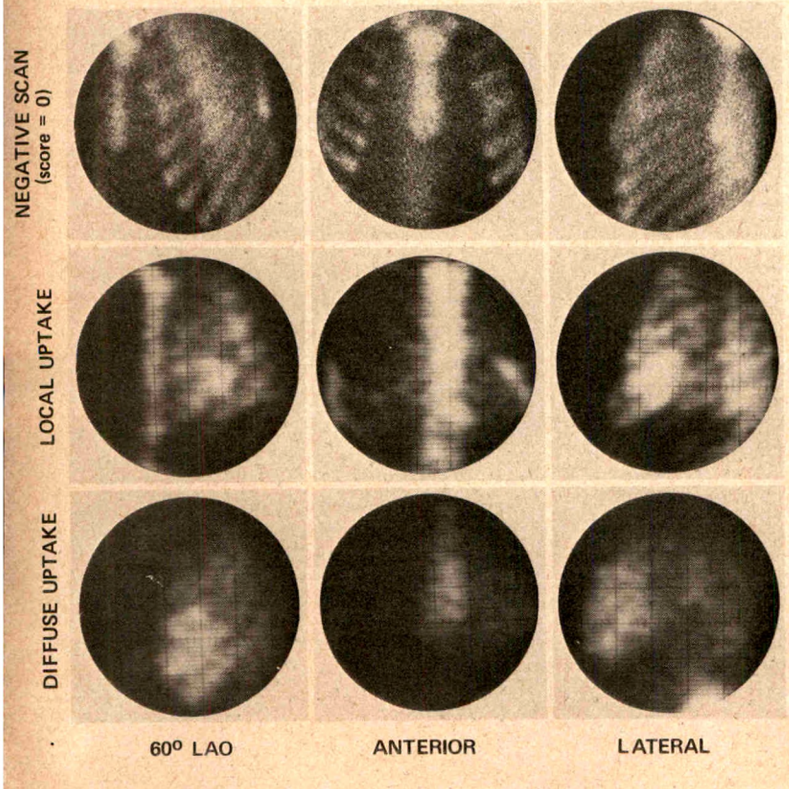


FIGURE 2. Top panel, three direct cathode ray images from a scintigram with no myocardial radionuclide uptake. **Middle panel,** a contrast-enhanced scintigram with localized anterior left ventricular wall uptake (score = 4.00, local, anterior). **Bottom panel,** another contrast-enhanced scintigram, showing diffusely increased radionuclide accumulation (seen best in the 60° left anterior oblique [LAO] projection).

underwent myocardial scintigraphy before scheduled bone scans were performed. The radiopharmaceutical dosage and imaging techniques used for these patients were the same as those for the patients with angina.

The existence of prior myocardial infarction was assessed on the basis of diagnostic Q waves or loss of R waves in serial 12 lead electrocardiograms. This method is relatively sensitive for detection of previous infarction and is the most accurate retrospective technique available.[9]

To obtain an estimate of the comparability of cardiac volumes in the normal subjects and the patients with angina, the cardiothoracic ratio on routine full inspiration posteroanterior chest X-ray film was measured. This ratio, as well as the transverse cardiac diameter and other measurements of the heart on chest roentgenogram, has been shown to correlate well with angiographically or directly measured cardiac volumes.[10–12] Although it does not give a precise measurement of cardiac volume in each patient, it serves as an adequate estimate for comparison of blood pool sizes of the two groups.

Imaging technique and interpretation: Myocardial scintigrams were obtained in anterior, 45° and 60° left anterior oblique and left lateral projections with a Picker Dyna scintillation camera (series 2C) with a 10,000-aperture, low energy, high resolution collimator. Sixty to 90 minutes after injection of 15 mCi of 99m-Tc pyrophosphate, images representing 200,000 scintillations were recorded on Polaroid® film directly from the cathode ray tube. Simultaneously the positioning information for these events was recorded by a digital computer system (Hewlett Packard 5407A) for later image processing.[13] A Versatek Matrix 1100A printer/plotter was used to produce two pseudogrey-shade hard copy displays of the data for each projection.[14,15] For the first display the scale was automatically set to cover the actual count range in order to minimize operator interference and, hence, bias. In the second display, contrast enhancement was achieved by removing a fraction of the picture elements considered to be nonspecific background and then evenly distributing the level of grey over the remaining elements (Fig. 1).

All scintigrams were read by four of us. Each reader was unaware of the others' intepretations and had no knowledge of the patients' identity, age or clinical status. The scintigrams were scored on an integral scale from 0 to 4. A score of 0 indicated no increase in myocardial uptake of pyrophosphate compared with background. A score of 4 signified sufficient myocardial uptake of the radionuclide to produce an image as dense as or more dense than bony uptake in the sternum. A score of 1 indicated faint myocardial uptake; scores of 2 and 3 corresponded to successively greater degrees of myocardial uptake (Fig. 2). Each reader's score was based on his evaluation of direct Polaroid oscilloscopic images, computer-processed Polaroid images and the Versatek grey scale hard copy printout of all four projections. A final score for each scintigram was obtained by averaging the four readers' responses. This method of scoring was used to reduce the impact of observer error, which can be considerable in the subjective interpretation of myocardial scintigrams (data submitted for publication from this laboratory). The scintigrams of the patients with angina and the control group were compared with two-tailed unpaired equal variance t tests.

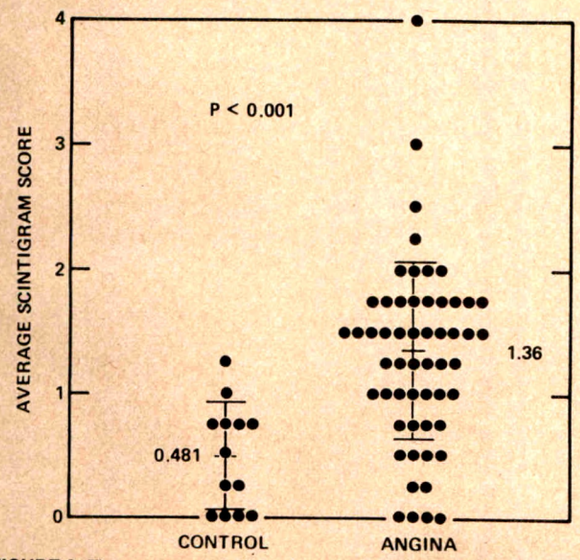


FIGURE 3. The average scintigraphic score for each of the 13 control patients and 55 patients with angina pectoris. The means and standard deviations for the two groups are indicated. The difference between scores in the two populations is statistically significant.

Results

Scintigraphic scores: The average scintigraphic scores of the 55 patients with stable angina and the 13 control patients were 1.36 and 0.48, respectively ($P < 0.001$) (Fig. 3). This significant difference was not produced artifactually by comparison of mean grades because the same level of significance for differences between patients with angina and the control group existed when the four readers' responses were considered separately.

To evaluate the contribution of blood pool to the scintigraphic score, the cardiac volume was estimated by determination of the cardiothoracic ratio on routine posteroanterior chest X-ray film. Although many other factors, such as initial blood volume and renal excretion

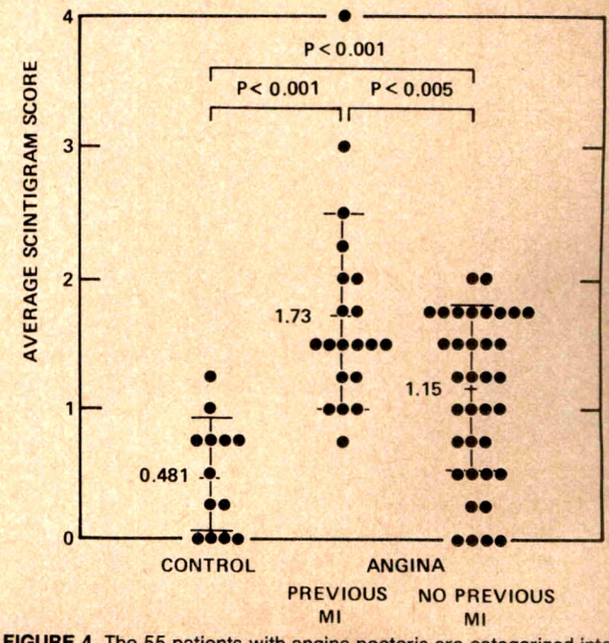


FIGURE 4. The 55 patients with angina pectoris are categorized into those with (no. = 19) and those without (no. = 36) electrocardiographic evidence of previous myocardial infarction (MI). These two groups of patients with angina were statistically different from one another and each differed from the control group.

TABLE II

Scintigraphic Scores for Patient Subgroups

	Patients (no.)	Mean Score	P Values		
Normal group	13	0.481	<0.001		
Group with stable angina	55	1.36		<0.001	
Previous MI	19	1.73	<0.005		<0.001
No previous MI	36	1.15			
One vessel disease	8	1.50	NS		
Two vessel disease	11	1.32			
Three vessel disease	23	1.42			
More than three vessel disease	13	1.31			

MI = myocardial infarction; NS = not significant; *P* = probability.

rate of pyrophosphate, might affect the quantity of radioactivity arising from the cardiac blood pool, ventricular volume is a major determinant. There was no relation between the roentgenographically determined heart size and the degree of pyrophosphate uptake in either group of patients, and the mean cardiothoracic ratios in the two groups did not differ significantly although six patients in the group with angina and none in the control group had a ratio greater than 50 percent.

The patients with angina were separated into those who did and did not have electrocardiographic evidence of previous myocardial infarction (Fig. 4). These two subgroups had significantly different mean scintigraphic scores (1.73 versus 1.15, $P < 0.005$). The scores in both groups differed independently from those of the control population ($P < 0.001$).

There was no significant difference among the mean scintigraphic scores of patients with one, two, three or more than three vessel* coronary artery disease (Table II). It should be noted that the patients with more than three major diseased vessels had a greater incidence of prior myocardial infarction as determined with electrocardiographic criteria.

Localized versus diffuse uptake: In addition to determining a score for each scintigram, the readers specified whether radionuclide uptake was localized or diffuse. Seventy percent of the 51 scintigrams with detectable radionuclide uptake in the group with angina showed diffuse uptake. All 10 scintigrams with average scores above 0 and below 1.01 showed diffuse uptake. Seventy-two percent (24 of 33) of the scintigrams graded 1.01 to 2.00 also demonstrated diffuse uptake. Uptake was localized in all six scintigrams with scores of 2.01 to 3.00, and was judged to be diffuse in the only two scintigrams with scores 3.00 or greater.

Three patients had average scintigraphic scores of 2.50 or greater. However, none of these three patients had historical, enzymatic or electrocardiographic evidence of recent myocardial infarction at the time they were studied, and none had a left ventricular aneurysm; as emphasized, all presented with stable angina pectoris.

* The classification "more than three vessel disease" refers to any combination of four or more lesions of 60 percent or more narrowing of luminal diameter in the right coronary artery, the circumflex coronary artery or one of its major marginal branches or the left anterior descending coronary artery or one of its large diagonal branches.

Discussion

The purpose of this investigation was to define the 99m-Tc pyrophosphate myocardial scintigraphic characteristics of patients with stable angina pectoris by comparing these patients with control patients without known heart disease. The interpretations of four observers using blinded reading techniques were averaged to determine a score for each scintigram. This method of scoring was chosen to remove the inaccuracy of scintigraphic interpretation introduced by observer variability. Studies of the accuracy and reproducibility of observations by interpreters of chest roentgenograms,[16–18] liver scintigrams[19] and myocardial scintigrams (data from this laboratory submitted for publication) have demonstrated a significant inaccuracy and variability of observers' readings because of the necessarily subjective nature of the interpretations. Although averaged readings of several interpretations might tend to obscure the observations of an especially skilled or insightful reader, this method should minimize the impact of observer error and interobserver disagreement.

Mechanism of increased pyrophosphate uptake in patients with stable angina: Our patients with stable angina pectoris had a mild increase in pyrophosphate uptake when compared with patients without heart disease. In addition, radionuclide uptake was greater in the 19 patients who had electrocardiographic evidence of previous myocardial infarction, but the degree of uptake did not correlate with the angiographic severity of the coronary disease. Our present knowledge of the mechanisms of myocardial pyrophosphate accumulation does not permit a definite explanation for the increased uptake we found. A relation between the presence of increased myocyte calcium content and pyrophosphate uptake has been established,[4] and it is known that calcium levels are elevated in infarcted myocardial cells.[7,8] In addition, ischemic but still viable myocardial cells in the experimental setting maintain an increased intracellular calcium concentration.[5,6] This might explain the increased scintigraphic radionuclide uptake detected in some patients with unstable angina pectoris[3] because they probably have a large quantity of ischemic yet viable myocardial cells. One might speculate that our patients had a degree of chronic myocardial ischemia sufficient to increase myocyte calcium concentration and promote pyrophosphate uptake. The presence of post-infarction myocardial scars (or perhaps microscarring in those patients without electrocardiographic evidence of prior infarction) could also have served as a locus of calcium accumulation in our patients. An alternate explanation might be that our patients had a continuously or intermittently ongoing mild myocardial necrosis that could only be detected scintigraphically. This latter speculation seems reasonable when one considers that

these patients had angina severe enough to warrant elective coronary bypass surgery; that is, their angina was uncontrolled by conventional medical therapy or characterized by intermittent episodes of prolonged pain or had seriously affected their quality of life.

Diffuse versus localized uptake: In the patients with stable angina, pyrophosphate uptake was judged to be diffuse in 70 percent of the 51 scintigrams with detectable uptake. Scintigrams with higher average scores showed localized uptake more frequently. All of the control patients with pyrophosphate uptake had diffuse accumulation. Diffuse radionuclide uptake has been described in subendocardial infarction[20,21] and has recently been reported in patients with unstable angina pectoris[3,22] and those with no known cardiac disease.[23] In the latter group, McLaughlin et al. questioned the significance of diffuse uptake and suggested the possibility of artifact introduced by blood pool radionuclide activity. Our patients with angina did not have increased cardiac volumes, as judged with the roentgenographic cardiothoracic ratio, to account for apparent excessive myocardial uptake. It is not clear why the pyrophosphate accumulation in our patients was predominantly diffuse.

Relation to myocardial infarction: Three patients without clinical evidence of acute myocardial infarction had advanced degrees of myocardial pyrophosphate uptake. These three patients had average scintigraphic scores of 2.50 (localized), 3.00 (diffuse) and 4.00 (diffuse). None of the three had diagnostic enzyme changes or electrocardiographic changes compatible with recent myocardial infarction and none had had a recent change in frequency or severity of chest pain. We have no explanation for this finding although high levels of pyrophosphate uptake have been described by other investigators in patients without evidence of myocardial infarction.[2,23] Pyrophosphate uptake is not specific for acute myocardial cellular ischemic injury[24,25] and does occur in disease states other than acute myocardial infarction, such as calcified left ventricular aneurysm.[24]

Implication: This study documents the existence of increased predominantly diffuse myocardial uptake of pyrophosphate in patients with stable angina pectoris. In addition, the strongly increased scintigraphic uptake in three patients with angina without acute myocardial infarction reemphasizes that pyrophosphate scintigraphy is not a completely specific test for acute myocardial infarction.

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Diagnostic Accuracy of Noninvasive Myocardial Imaging for Coronary Artery Disease: An Electrocardiographic and Angiographic Correlation

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From 1972 through 1975, a total of 781 noninvasive myocardial imaging studies were performed at rest and with exercise in 345 patients with use of potassium-43 or rubidium-81, or both. Resultant images were interpreted by three observers unaware of the clinical data. One hundred sixty of these patients underwent coronary angiography and were arbitrarily classified on the basis of percent narrowing of luminal diameter into those with coronary arterial obstruction of 70 percent or greater (hemodynamically significant disease) or less than 70 percent obstruction (insignificant disease) for the purposes of determining sensitivity and specificity of noninvasive myocardial imaging. Fifty-one of the 62 patients with angiographically insignificant coronary artery disease had normal imaging studies (specificity 82 percent). The 98 patients with angiographically significant coronary artery disease had 81 abnormal imaging studies (sensitivity 83 percent). When patients with myocardial infarction were excluded, the sensitivity rate of myocardial imaging was 75 percent, whereas that of standard electrocardiographic exercise tolerance testing was 72 percent. The sensitivity rate in identifying angiographic coronary stenosis in noninfarcted vascular beds was 88 percent when the results of myocardial imaging and electrocardiographic exercise testing were combined. These data present a standard for comparing future techniques of myocardial imaging at rest and with exercise.

Noninvasive myocardial imaging after the intravenous injection of radioactive tracers is becoming more frequently utilized as a procedure for evaluating patients for the presence or absence of coronary artery disease.[1–6] When patients are studied at rest a reduction in regional tracer activity in the resultant myocardial images corresponds to areas of fibrous scar due to myocardial infarction. When radioactive tracers are injected intravenously after the onset of fatigue or angina pectoris during exercises, a region of decreased radioactivity in subsequent myocardial images identifies an ischemic vascular bed beyond a hemodynamically significant coronary arterial obstruction (Fig. 1). Potassium-43 and rubidium-81 have been utilized for this purpose because of their extremely rapid myocardial extraction, high intracellular accumulation rate and relatively short half-life. Since 1972 we have used these agents to perform 781 imaging studies at rest and with exercise in 345 patients. To evaluate the sensitivity and specificity of this technique in assessing the presence of coronary artery disease, we correlated the results of noninvasive myocardial imaging with the electrocardiographic findings in 160 of these patients who also underwent angiographic studies.

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Methods

The results of myocardial imaging and stress electrocardiography were assessed in 160 patients who were also studied with angiography as part of a clinical evaluation for coronary artery disease. Patients undergoing imaging studies represented a proportional sampling of all patients evaluated angiographically at this medical center from September 1972 through October 1975. Patients with left bundle branch block were excluded because of the unique imaging characteristics of these subjects reported elsewhere.[7] No correlations were attempted in patients who had prior aortocoronary bypass surgery.

Stress electrocardiography and imaging were performed utilizing a maximal graded treadmill exercise test and continuous electrocardiographic monitoring with a standard multilead system. The criterion for a positive electrocardiographic exercise test was flat or downsloping S-T depression of 1 mm for at least 0.08 second on three or more consecutive beats. Patients exercised to the point of fatigue or chest pain, when 1 mCi of potassium-43 or 2 mCi of rubidium-81 was injected intravenously. Exercise was continued for an additional 30 to 45 seconds after which the patient was promptly transported to the adjacent nuclear medicine laboratory where duplicate images were obtained in the anterior and 45° left anterior oblique positions using either a standard rectilinear scanner with a 5 inch (12.7 cm) crystal and both 3 inch and 5 inch (7.6 and 12.7 cm) focused high energy collimators (133 patients) or a scintillation camera (27 patients). Scintillation camera imaging was performed using a pin-hole collimator and a 3 mm insert. Images were obtained on Polaroid® film and were not computer-processed. Additional lead shielding was utilized as previously described.[8] Details of the imaging techniques and dosimetry have been published elsewhere.[4,9] Images in the resting state were obtained 3 to 6 days later after the patients had had a 12 to 14 hour fast and had stood erect for 10 to 15 minutes to reduce gastric and hepatic tracer uptake and background interference. The studies were interpreted by three experienced observers unaware of the clinical data in each case.

Selective coronary cineangiography and left ventriculography were performed with the brachial arteriotomy or percutaneous femoral arterial approach, usually within 2 weeks of the imaging studies. Coronary arteriograms were filmed at 60 frames/sec on 35 mm film using both the 6 and 9 inch (15.2 and 22.9 cm) fields of a variable field image intensifier. Biplane left ventricular cineangiography was accomplished after the intracavity injection of 45 cc of contrast medium over 3 seconds. Angiograms were reviewed by at least three staff cardiologists and an average luminal narrowing was determined for each angiographic lesion. For purposes of this study an average luminal narrowing of 70 percent or greater was arbitrarily considered hemodynamically significant.[10] A diagnosis of myocardial infarction was accepted when regional akinesia or dyskinesia was noted in the distribution of a totally occluded coronary artery in a patient with an appropriate clinical history.

Angiographic interpretation in the 160 cases yielded five patient groups: Group I—normal coronary arteries, 50 patients; Group II—hemodynamic insignificant coronary artery disease, 12 patients; Group III—significant coronary artery disease without myocardial infarction, 50 patients; Group IV—significant coronary artery disease with myocardial infarction, 27 patients; and Group V—significant coronary artery disease with myocardial infarction plus additional coronary disease involving noninfarcted myocardium, 21 patients.

TABLE I

Decision Matrix

	Coronary Artery Disease	Normal
Positive test =	a	c
Negative test =	b	d

Sensitivity = a/(a + b).
Specificity = d/(c + d).

a = true positive results; b = false negative results; c = false positive results; d = true negative results.

Significant obstructive coronary artery disease was considered present if the patient had a prior myocardial infarction or an angiographically significant coronary obstruction, or both. Subjects not meeting these criteria were considered to have normal coronary arteries. With use of these criteria the formulas in Table I were utilized to determine the sensitivity and specificity of myocardial imaging and stress electrocardiography in identifying the presence of angiographically significant obstructive coronary artery disease.

Results

Myocardial Imaging

Comparison of images at rest and during exercise: Diagnostic studies were obtained in all patients and no untoward side effects were encountered in the course of the study. The 160 patients were classified into one of four categories on the basis of a comparison of the images obtained at rest and during exercise: normal homogeneous tracer distribution at rest and with exercise (no. = 68); normal images at rest and a regional defect with exercise (no. = 47) (Fig. 1); an abnormal defect at rest unchanged with exercise (no. = 45); and an abnormal image at rest but an additional regional defect observed with exercise (no. = 17). Of the 50 patients in Group I with angiographically normal coronary arteries, 8 had an abnormal image with exercise and 42 a normal image (Table II). Of the 12 patients in Group II with angiographically insignificant coronary artery disease, 9 had a normal and three an abnormal study with exercise. All patients in Groups I and II had a normal image at rest. The 50 patients in Group III had one, two or three vessels with 70 percent or more luminal narrowing but had no prior myocardial infarction. All 50 had a normal image at rest, but 36 had an abnormal image with exercise; the other 14 studies remained normal with exercise and were interpreted as negative for significant coronary artery disease. Twenty-four of the 27 patients in Group IV with myocardial infarction had abnormal images both at rest and with exercise; the remaining 3 had normal studies at rest and with exercise. All 21 patients in angiographic Group V (myocardial infarction and at least one significant obstructive lesion in one or more noninfarcted beds) had abnormal images in the area of infarction both at rest and with exercise. Seventeen of these 21 patients had new image defects on exercise in addition to the defects demonstrated at rest.

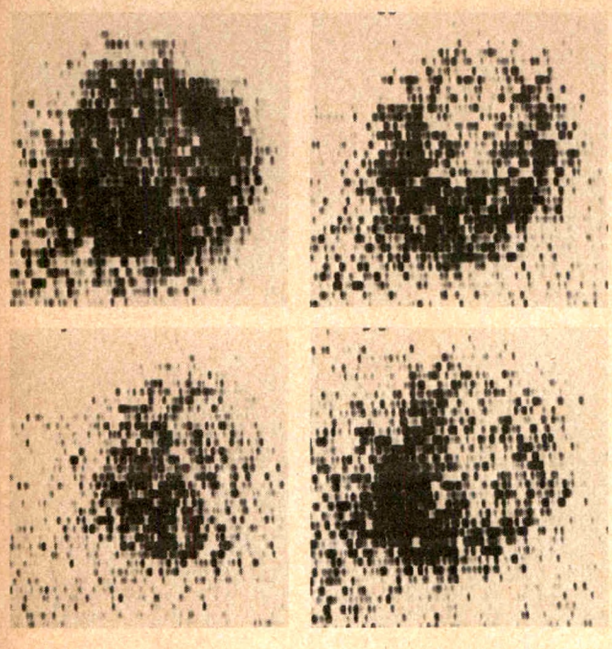


FIGURE 1. Rubidium-81 myocardial scans obtained at rest (**upper panels**) and after exercise to angina pectoris (**lower panels**). The central defect (corresponding to the left ventricular cavity) noted at rest in both the anterior (ANT) and left anterior oblique (LAO) positions is somewhat more well defined than usual. The extensive posterolateral defect seen after exercise is consistent with the 90 percent proximal obstruction of the left circumflex artery demonstrated on coronary angiography.

Sensitivity and specificity of myocardial imaging: The sensitivity and specificity of imaging in determining the presence or absence of angiographically significant coronary artery disease were analyzed with use of the specified formula. The overall sensitivity rate in identifying significant coronary disease was 83 percent (81/81 + 17) and the specificity rate in excluding coronary artery disease was 82 percent (51/51 + 11). Diagnostic accuracy was greatest (94 percent) in identifying a prior myocardial infarction (Groups IV and V) and was least (72 percent) in identifying patients with coronary obstruction greater or equal to 70 percent luminal narrowing who had no prior myocardial infarction (Group III). The sensitivity rate of myocardial imaging in determining the presence of additional regions of ischemia in patients with prior myocardial infarction was 81 percent (Group V) and, when these patients were combined with patients with coronary obstruction without infarction (Group III), the sensitivity rate in identifying coronary luminal narrowing greater than or equal to 70 percent in noninfarcted vascular beds was 75 percent. There were 127 noninfarcted vascular beds with angiographic obstruction of 70 percent or more in the 71 patients in Groups III and V. Of these, 41 percent were correctly localized with imaging; accuracy was greatest in identifying left circumflex lesions. Regions of myocardial infarction were correctly localized in 85 percent of the 48 patients in Groups IV and V.

Nine patients from Group III with stable angina pectoris were subjected to one imaging study at rest and four during exercise over a 13 week period. All nine demonstrated a significant image defect with exercise. The repeat exercise studies were reproducible as interpreted by visual analysis.

Electrocardiography

Four electrocardiographic groups comparable with the four imaging groups could be identified: a normal resting electrocardiogram with no significant S-T changes with exercise (no. = 48); a normal resting electrocardiogram with significant exercise-induced S-T changes (no. = 67); an electrocardiogram with diagnostic Q waves at rest and no S-T changes with exercise (no. = 22); and Q waves at rest but the additional development of S-T changes with exercise (no. = 23). An electrocardiogram with equivocal or nondiagnostic alter-

TABLE II

Results of Electrocardiographic and Myocardial Image Interpretation in Relation to Angiographic Findings in 160 Patients

Angiographic Group	Patients (no.)	Electrocardiographic Results		Imaging Results	
		Abnormal Q Waves	Diagnostic S-T Changes With Exercise	Abnormal Images At Rest	Abnormal Images With Exercise
I. (normal coronary arteries)	50	0	26	0	8
II. (coronary narrowing <70%)	12	0	5	0	3
III. (coronary stenosis ≥70% without myocardial infarction)	50	0	33	0	36
IV. (myocardial infarction without additional coronary stenosis ≥70%)	27	25	5	24	24*
V. (myocardial infarction with additional coronary stenosis ≥70%)	21	20	18	21	21(17)†

* No significant change noted when comparing exercise images with those obtained at rest.
† With exercise 17 of these 21 patients demonstrated regional image defects in addition to those obtained at rest.

ations was considered normal for purposes of this study.

When the criteria for sensitivity and specificity were applied to electrocardiographic interpretation, the electrocardiogram had on overall sensitivity rate of 80 percent in identifying significant coronary artery disease (Table III). The specificity rate of the electrocardiogram in excluding significant coronary artery disease (a normal resting 12 lead electrocardiogram and the absence of exercise-induced S-T abnormalities) was 50 percent. As with imaging, electrocardiographic accuracy was greatest (94 percent) in identifying the presence of a myocardial infarction (Groups IV and V) and was least (66 percent) in identifying coronary obstruction in the absence of a prior myocardial infarction (Group III) (Table II). The sensitivity rate in determining the presence of additional coronary stenosis in patients with prior infarction was 86 percent. When these patients were combined with those having coronary stenosis but no prior infarction, the sensitivity rate of stress electrocardiography in identifying coronary arterial narrowing of 70 percent or more in noninfarcted vascular beds was 72 percent.

TABLE III

Comparison of Electrocardiographic Testing With Noninvasive Myocardial Imaging in Identifying Angiographically Significant Coronary Artery Disease

	Sensitivity Rates			Specificity Rate
Test	MI Only	Excluding MI*	Overall	Overall
NIMI	94%	75%	83%	82%
ECG	94%	72%	80%	50%
NIMI + ECG	97%	88%	92%	45%

*Sensitivity in identifying coronary stenosis in noninfarcted vascular beds by a significant change with exercise, the image observed at rest.

ECG = electrocardiography at rest and with stress testing; MI = myocardial infarction; NIMI = noninvasive myocardial imaging at rest and with exercise.

Combined Studies

Although the sensitivity achieved using either myocardial imaging or electrocardiographic testing was comparable, the standards of electrocardiographic interpretation required to obtain this degree of sensitivity resulted in a low rate of specificity. On the other hand, standards for myocardial image interpretation resulted in a specificity commensurate with the sensitivity. Because imaging with exercise is performed in conjunction with a stress electrocardiogram, these tests were assessed for a possible complementary value in identifying coronary artery disease. Using an abnormal exercise image or stress electrocardiogram as the criterion for an abnormal test and requiring both the exercise image and stress electrocardiogram to be normal for an interpretation of normal arteries, we found an 88 percent sensitivity rate in identifying coronary occlusive disease of 70 percent or more in noninfarcted vascular beds (Groups III and V) (Table III). A sensitivity rate of 97 percent in identifying myocardial infarction was obtained when either an abnormal scan at rest or classic Q waves in the resting electrocardiogram were utillized (Groups IV and V). The overall sensitivity rate in identifying significant coronary artery disease was 92 percent but, primarily because of the number of false-positive stress electrocardiograms, the specificity rate of 45 percent was little different from that of exercise tolerance testing alone in identifying patients with coronary artery disease.

Discussion

We propose the use of noninvasive imaging as an objective screening test for identifying significant coronary artery disease, confirming suspected myocardial infarction, following up patients subjected to saphenous vein bypass surgery and evaluating the long-term disease process in patients with established coronary artery disease. The sensitivity and specificity of this technique are quite good and clearly superior to those of any other available noninvasive tests for the purposes noted. The reproducibility has been excellent in the small number of patients subjected to multiple studies using identical techniques. The additional benefit of localizing the involved vascular beds has at times been helpful, but the

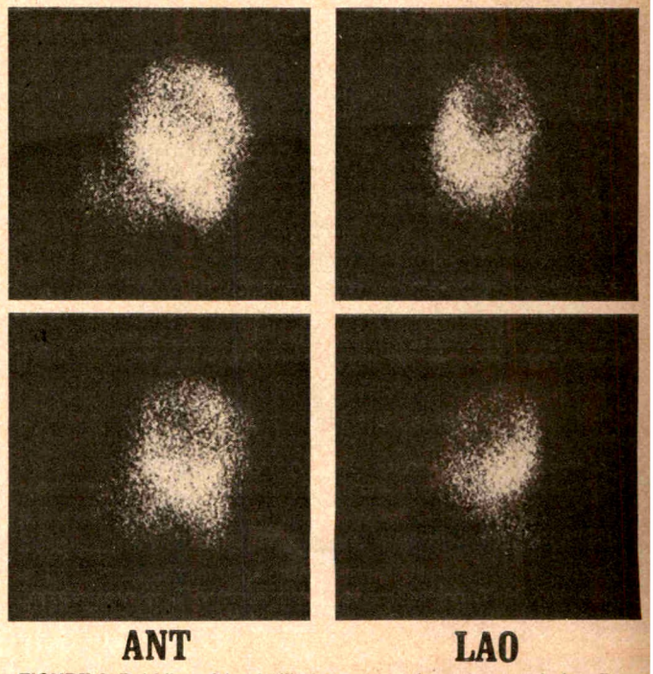


FIGURE 2. Rubidium-81 scintillation camera images recorded on Polaroid film at rest (**upper panels**) and with exercise (**lower panels**) in a patient with severe angina pectoris. The central defect corresponding to the left ventricular cavity in both views at rest is typical of that seen in normal camera images. With angina pectoris after exercise, a large anterior defect is noted in both the anterior (ANT) and left anterior oblique (LAO) positions. Coronary arteriograms revealed a subtotal obstruction of the proximal left anterior descending artery commensurate with these findings.

accuracy in localizing and quantitating obstructive lesions has been disappointing.

Noninvasive myocardial imaging is safe, producing no untoward side effects and requiring a small radiation dose. The good overall sensitivity rate (83 percent) was comparable with the 80 percent sensitivity rate of electrocardiographic stress testing. The respective specificity rates were 82 percent for myocardial imaging but only 50 percent for electrocardiographic testing. The sensitivity rate in identifying significant coronary artery disease when combining the results of noninvasive myocardial imaging with electrocardiographic findings was 92 percent, but the frequent occurrence of false-positive electrocardiographic stress tests held the specificity rate to less than 50 percent when results were combined.

Future applications and improvements in diagnosis: Recent changes in techniques have improved the diagnostic accuracy of noninvasive myocardial imaging, and newer tracers promise to make the procedure more readily available. In December 1973, rubidium-81 was substituted for potassium-43 as our primary imaging agent and concurrently a 5 inch (12.7 cm) focused high energy collimator was substituted for the previously utilized 3 inch (7.6 cm) high energy focused collimator for imaging in the left anterior oblique projection. These changes in technique and radionuclide increased the overall sensitivity rate from 80 to 90 percent. This improvement is significant because the earlier studies were more likely to be performed in patients with well defined disease in order to establish the accuracy of the technique. Later tests were performed for diagnostic purposes as part of the clinical evaluation of patients when the presence or absence of significant coronary artery disease was in question.

The capability of obtaining diagnostic scintiphotographs with rubidium-81 and a scintillation camera without contrast enhancement was demonstrated by the excellent results obtained in 27 subjects (Fig. 2). Although the scintillation camera studies are comparable we have preferred the rectilinear scanner because image interpretation has been easier and more consistent, and the additional lead shielding required for satisfactory imaging with these agents had been cumbersome. All studies in this report were performed with potassium-43 or rubidium-81 as the radionuclide. Thallium-201 has generally replaced these earlier perfusion radionuclides for myocardial studies[11–15] because it has an energy spectrum more suitable for conventional scintillation camera imaging and a longer physical half-life. Use of this radionuclide with an appropriately tuned scintillation camera definitely enhances resolution. We currently utilize thallium-201 and the scintillation camera for noninvasive myocardial imaging at rest and with exercise. Although the number of studies is limited, our initial results are comparable with those obtained with potassium-43 and rubidium-81 using the rectilinear scanner. Potassium-43 and rubidium-81 will not be used in the future. The general technique of imaging at rest and during exercise certainly will. These initial data present a standard against which future studies with different radionuclides should be compared.

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Echocardiographic Diagnosis of Left Anterior Descending Coronary Artery Disease

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To determine the usefulness of the standard echocardiogram in the diagnosis of left anterior descending coronary artery disease proximal or distal to the first septal branch, coronary arteriograms and echocardiograms were performed in 77 patients with a chest pain syndrome. Seventy-nine percent of patients with proximal disease (15 of 19) had an abnormal septal motion measured as a posterior wall/interventricular septal (PW/IVS) excursion ratio greater than or equal to 2.5 compared with 10 percent of patients with distal disease (2 of 20) who had abnormal septal motion. Only 5 percent of patients without obstructive disease of the left anterior descending coronary artery (2 of 38) had abnormal septal motion. Proximal disease was found in 79 percent with abnormal septal motion in the echocardiogram (15 of 19) but in only 7 percent of patients with normal septal motion (4 of 58). Therefore, abnormal septal motion as measured by the PW/IVS excursion ratio in the echocardiogram is a useful index for the diagnosis of disease of the left anterior descending coronary artery when that disease is proximal to the first septal branch.

Echocardiography is currently being used to evaluate left ventricular size, volume and function.[1–8] The motion of the interventricular septum has been studied in various disease states[9,10] including atrial septal defect,[11] rheumatic involvement of the mitral and aortic valve,[1,5] idiopathic hypertrophic subaortic stenosis,[5,12] primary myocardial disease,[13] left bundle branch block,[14–16] constrictive pericarditis[17] and coronary artery disease.[13,18–21] Diminished or abnormal septal motion in some patients with left anterior descending coronary artery disease has been reported.[19–21] However, a correlation between septal motion and the precise location of significant obstruction in the left anterior descending coronary artery has not previously been reported. Measurement of septal motion in the standard echocardiogram permits noninvasive evaluation of the functional state of the first portion of the muscular septum. In patients with coronary artery disease, diminished, absent or abnormal septal motion should imply impaired circulation to that region of the heart. In this study we attempted to determine the usefulness of the standard time-motion echocardiogram in diagnosing left anterior descending coronary artery disease either proximal or distal to the origin of the first septal branch.

Material and Methods

Seventy-seven patients with a mean age of 49 years (range 30 to 73 years) who were referred to the cardiovascular unit of the Peter Bent Brigham Hospital during the 21 months from September 1972 to June 1974 for evaluation of a chest pain syndrome were studied in retrospective fashion. The 77 patients formed a consecutive subset of patients drawn from the larger pool of all patients studied in the laboratory. All patients with valvular or congenital heart disease or known primary myocardial disease were excluded. Also excluded were patients who had

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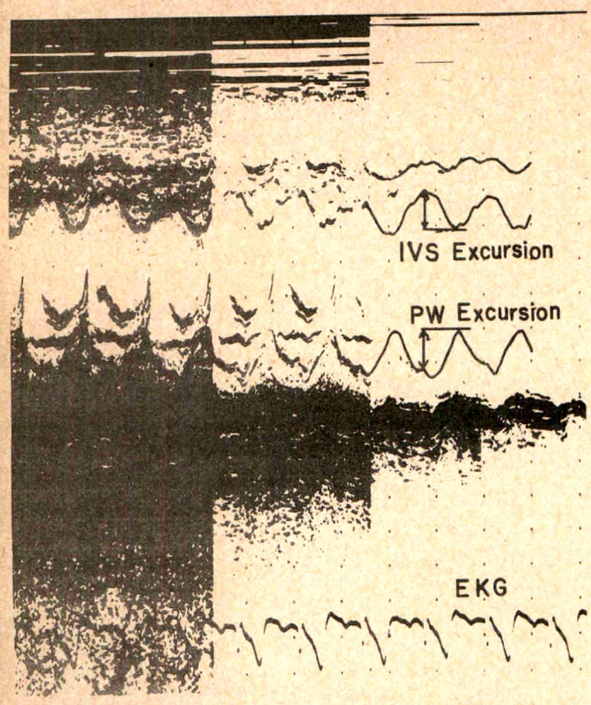


FIGURE 1. Method of measuring endocardial excursions. The normal echocardiogram of the interventricular septum (IVS) and posterior wall (PW) is shown at **left** with the corresponding diagram traced from it at **right.** EKG = electrocardiogram.

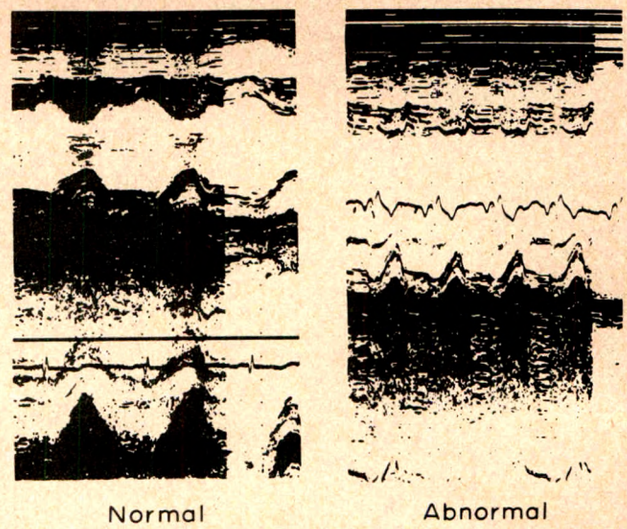


FIGURE 2. Representative echocardiograms. On the **left,** an echocardiogram with both normal interventricular septal (IVS) and posterior wall (PW) excursion and normal PW/IVS ratio; on the **right,** an echocardiogram with both abnormal interventricular septal excursion and an abnormal PW/IVS ratio.

no echocardiographic studies and those whose echocardiographic visualization of the interventricular septum and posterior wall was not sufficient to allow accurate analysis (approximately 10 to 15 percent). Each patient in this series had an echocardiogram that allowed simultaneous visualization of the interventricular septal and posterior wall endocardium in the standard recording position below the level of the mitral valve.[1,22] Each patient had coronary arteriograms that allowed detailed analysis of the presence or absence of atherosclerotic disease either proximal or distal to the first septal branch of the left anterior descending coronary artery.

Echocardiography: Echocardiograms were obtained within 36 hours before cardiac catheterization with use of a Unirad series C Sonograph; they were recorded with Polaroid® photographs of the M-mode display early in the 20 month study period and on a Tektronix strip chart recorder when that instrument became available. A monitor lead electrocardiogram was simultaneously recorded for timing purposes. A 13 mm diameter nonfocused 2.25 megahertz transducer was used. Patients were studied while in the supine position with the thorax elevated to an angle of approximately 30°. When adequate visualization was not obtained in this position, patients were turned to a slight left lateral position that usually allowed better simultaneous visualization of the interventricular septum and posterior wall. Recording of the interventricular septal and posterior wall endocardium was performed in a standard manner just inferior and lateral to the mitral valve with the transducer approximately perpendicular to the chest wall.[1,22] The portion of septum visualized using this technique represents the upper portion of the muscular septum. The lower or apical portions of the septum were not studied. The echocardiograms were analyzed and reviewed independently by at least three of us.

Maximal excursion of the interventricular septal and posterior wall endocardium from end-diastole to end-systole was measured to the nearest 1 mm (Fig. 1). In the rare instances when interobserver variation in measurement occurred, a consensus was reached; in no case was there a variation of more than 1 mm. Normal values in our laboratory for endocardial excursion of the interventricular septum and posterior wall are 5 to 9 mm and 10 to 15 mm, respectively. Diminished septal motion is defined as a maximal excursion of 4 mm or less. When septal motion was not detectable, an arbitrary value of 1 mm was assigned as the maximal septal excursion to permit formation of a numerical ratio of the maximal excursion of the posterior wall to the maximal excursion of the interventricular septum (PW/IVS ratio). In the four patients with asynchrony of septal and posterior wall motion, the maximal excursion value was used regardless of timing. After initial review of the data, it was decided to form a ratio of the maximal endocardial excursion of the posterior wall (PW) to the maximal endocardial excursion of the interventricular septum (IVS). The value of this ratio was expressed to the nearest 0.1, and a ratio of 2.5 or greater was considered abnormal. Figure 2 shows representative echocardiograms of patients with both normal and abnormal values for excursion and PW/IVS ratio.

Coronary arteriography: Selective coronary arteriograms were obtained in multiple projections using either the Judkins or Sones technique and were recorded on 16 mm film with either a 6 inch (15.24 cm) dual field General Electric or Siemens image intensification fluoroscopic system. The coronary arteriograms were analyzed without knowledge of the echocardiograms and were reviewed independently by at least three of us. Obstructions to the three major vessels and their branches were noted. In the few instances of interobserver variation in interpretation of the angiograms, a consensus was reached. Obstructive lesions were classified as significant if there was greater than 75 percent narrowing of luminal diameter.

Patients were classified into three groups on the basis of location and distribution of coronary arterial obstruction.

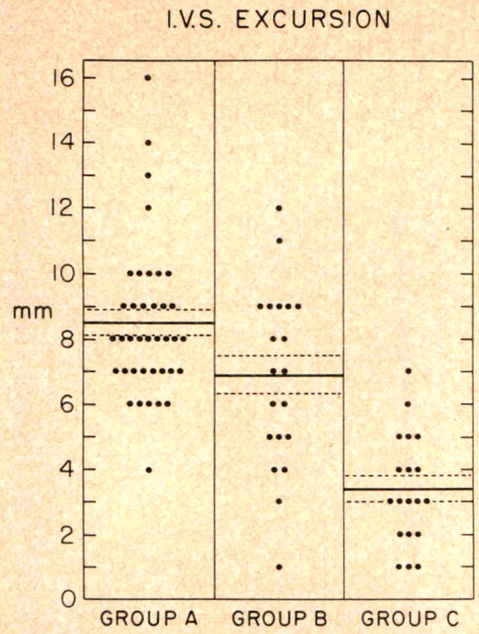


FIGURE 3. Interventricular septal (I.V.S.) excursion in the three groups of patients. Group A (no obstructive disease in the left anterior descending coronary artery), Group B (more than 75 percent obstruction *distal* to the first septal branch), Group C (more than 75 percent obstruction *proximal* to the first septal branch). The vertical axis represents measured endocardial excursion of the interventricular septum in millimeters. **Solid lines** represent the mean excursion for each group; **dotted lines** represent the standard error of the mean.

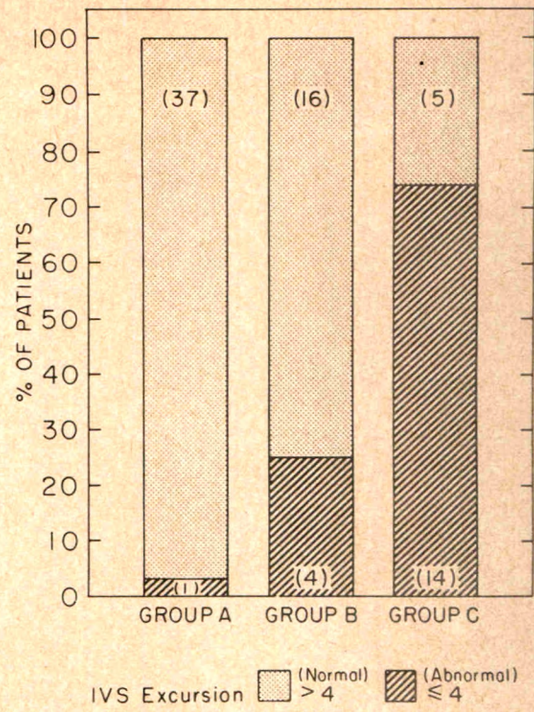


FIGURE 4. Prevalence of normal and abnormal septal (IVS) excursion in Groups A, B and C. Numbers in parentheses refer to number of patients.

Group A consisted of 38 patients without obstructive disease in the left anterior descending coronary artery; this group included 16 patients with entirely normal coronary arteries. Group B consisted of 20 patients with greater than 75 percent obstruction of the left anterior descending coronary artery distal to the origin of the first septal branch. Group C consisted of 19 patients with greater than 75 percent obstruction of this artery proximal to the origin of the first septal branch; this group included 3 patients who also had significant obstruction of the left main coronary artery. There was no significant difference among the three groups in distribution and extent of obstructive lesions in other major coronary arteries or branches.

Numerical data were analyzed using the Student t distribution.

Results

Interventricular septal motion (Fig. 3): There were 58 patients with normal septal motion (maximal excursion more than 4 mm) and 19 patients with diminished or absent septal motion (maximal excursion 4 mm or less). Forty-six percent of patients (18 of 39) with disease in the left anterior descending coronary artery either proximal (Group C) or distal (Group B) to the first septal branch had abnormal septal motion as defined. A comparison of the mean values in each of the three angiographic groups shows that patients in these two groups had a significantly lower value for mean septal excursion than those with no disease in the left anterior descending coronary artery (Group A) ($P < 0.001$). In addition, the mean septal excursion was significantly lower in patients with proximal obstructive disease (Group C) than in those with distal obstructive disease (Group B) ($P < 0.001$). However, there was overlap among individual data points in each of the three groups. Of note, all five patients in Group A and all six patients in Group B with less than 75 percent narrowing of luminal diameter proximal to the first septal branch had normal septal excursion.

Figure 4 shows that there was a relation between proximal left anterior descending coronary artery disease (Group C) and the prevalence of abnormal septal excursion. Seventy-four percent of patients in Group C had an abnormal septal excursion compared with only 25 percent of patients in Group B (distal obstruction) and 3 percent of patients in Group A (no obstruction). Figure 4 also shows that 74 percent of patients with abnormal septal excursion had proximal left anterior descending coronary artery disease compared with only 9 percent of patients with normal septal excursion.

Posterior wall excursion (Fig. 5): The mean values for posterior wall excursion in patients in Groups B and C were slightly lower than the mean value in patients without disease of the left anterior descending coronary artery (Group A) ($P < 0.05$). The marked scatter of individual data points makes it difficult to characterize the three groups on the basis of posterior wall excursion alone. Five of six patients in Groups B and C with significantly decreased posterior wall excursion (8 mm or less) had obstructive coronary artery disease involving all three vessels.

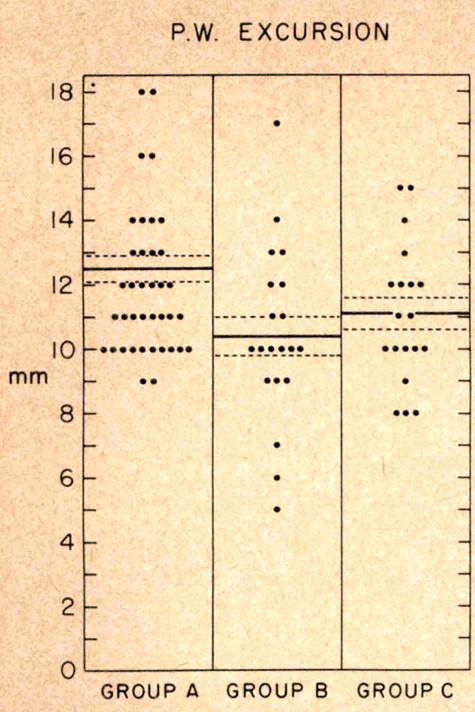


FIGURE 5. Posterior wall (P.W.) excursion in the three patient groups. The vertical axis represents measured endocardial excursion of the posterior wall in mm. Other symbols as in Figure 3.

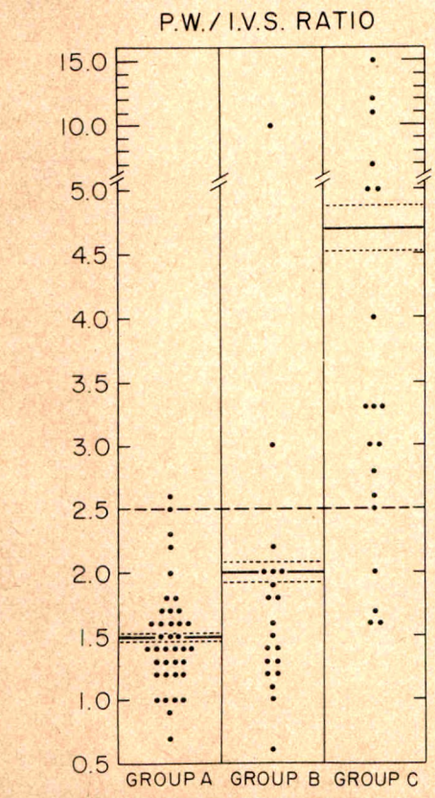


FIGURE 6. Posterior wall/interventricular (P.W./I.V.S.) excursion ratio in the three patient groups. The **heavy dotted line** represents the value 2.5, chosen as the lowest abnormal value (see text). The vertical axis represents numerical values obtained by forming the ratio of posterior wall to interventricular septal excursions as described in the text. Other symbols as in Figure 3.

PW/IVS ratio (Fig. 6): There were 58 patients with a normal posterior wall/interventricular septal excursion ratio (PW/IVS ratio less than 2.5) and 19 patients with an abnormal PW/IVS ratio (2.5 or greater). The mean of this ratio for patients with proximal disease of the left anterior descending artery (Group C) was significantly higher than both the mean ratio for patients without disease in this artery (Group A) ($P < 0.005$) and the mean ratio for patients with distal disease (Group B) ($P < 0.005$). There was no significant difference between the mean values in patients without left anterior descending coronary artery disease (Group A) and patients with distal disease (Group B) ($P > 0.05$).

There was a relation between proximal left anterior descending coronary artery disease (Group C) and the prevalence of an abnormal PW/IVS ratio (Fig. 7). Seventy-nine percent (15 of 19) of patients in Group C had an abnormal ratio. The four patients with a normal ratio had extensive collateral vessels to the left anterior descending coronary artery through septal vessels from the right coronary artery. In contrast, only 10 percent (2 of 20) of patients in Group B (distal obstruction) and 5 percent (2 of 38) of patients in Group A (no disease) had an abnormal ratio. One of the two patients in Group B with an abnormal ratio had marked elevation of left ventricular end-diastolic pressure in the absence of obstructive coronary artery disease and the other had right ventricular dilatation without a detectable shunt. The data in Figure 7 also demonstrate that 79 percent of patients with an abnormal PW/IVS ratio had proximal left anterior descending coronary artery disease

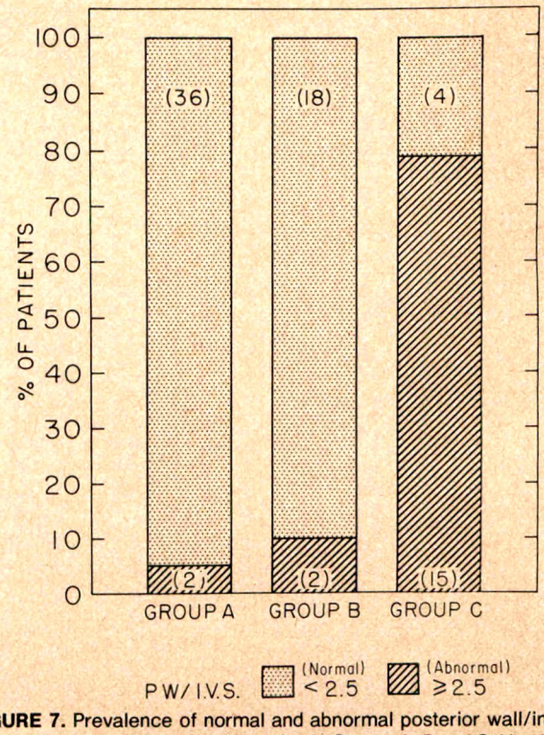


FIGURE 7. Prevalence of normal and abnormal posterior wall/interventricular (PW/I.V.S.) excursion ratios in Groups A, B and C. Numbers in parentheses refer to number of patients.

whereas only 7 percent of patients with a normal ratio had such disease.

Discussion

In this study, 46 percent of 39 patients with significant left anterior descending coronary artery disease had abnormal septal excursion on echocardiography. When left anterior descending coronary disease was characterized by whether the obstruction was proximal or distal to the first septal branch, a clear separation of patients occurred. Seventy-four percent of those with proximal disease and only 25 percent of those with distal disease had abnormal septal excursion.

Relation between left anterior descending coronary artery disease and septal motion: There is a direct relation between the location and extent of coronary occlusive disease and the location and degree of left ventricular asynergy.[23–29] James[30] demonstrated that the blood supply to the muscular septum is primarily from branches of the left anterior descending coronary artery. Diminished, flat or paradoxical septal motion has been associated with left anterior descending coronary artery disease. Jacobs et al.[19] reported that 79 percent of patients (30 of 38) with greater than 75 percent obstruction of the left anterior descending coronary artery had abnormal septal excursion. In a preliminary report, Brown et al.[20] reported that 94 percent of patients (30 of 32) with greater than 50 percent obstruction of the left anterior descending coronary artery had abnormal septal excursion. However, the location of the obstruction in the left anterior descending coronary artery is not stated in either study. In a preliminary report, DeMaria et al.[21] reported that 76 percent of patients (33 of 43) with greater than 75 percent obstruction in or prior to the proximal one third of the left anterior descending coronary artery had abnormal septal motion; although they do not indicate the relation of obstructions to the first septal branch, their results are similar to our findings. The high degree of correlation between proximal obstruction angiographically and abnormal septal motion echocardiographically strongly suggests that the portion of ventricular septum visualized is indeed perfused primarily by the large first septal branch of the left anterior descending coronary artery and not by more distal portions of this vessel or its branches.

Because wall motion abnormalities in coronary artery disease tend to be regional and there may be compensatory hyperkinetic motion of some segments in response to hypokinetic or akinetic motion of other segments, the ratio of posterior wall/interventricular septal maximal excursion (PW/IVS ratio) was used to emphasize or amplify abnormalities in septal motion. Seventy-nine percent of patients with proximal (Group C) and only 10 percent of those with distal (Group B) left anterior descending coronary artery disease had an abnormal PW/IVS ratio. There were two patients with abnormal septal excursion and a normal ratio in Group A (no significant obstruction) and two patients with normal septal excursion and an abnormal ratio, one each in Group A and Group C. In three of these four patients the coronary anatomy was properly categorized with the PW/IVS ratio and not with septal excursion. An abnormal PW/IVS ratio appeared in this study to be a better indicator of proximal left anterior descending coronary artery disease than did abnormal septal excursion alone.

Causes for discordant echocardiographic and angiographic findings: Improper categorization of the location of left anterior descending disease occurs in some cases. Possible reasons for discordance when comparing the echocardiographic functional anatomy of the interventricular septum and coronary arteriographic abnormalities include: (1) The portion of interventricular septum visualized in the echocardiogram may not be that portion supplied by the first septal branch (this may be one reason for the false positive findings in Group B [patients with distal disease]). (2) The combination of a hypokinetic posterior wall and a hypokinetic interventricular septum may occur, resulting in a normal PW/IVS ratio. (3) The arteriogram may demonstrate blood supply to the upper muscular septum occurs by a route other than the first septal branch of the left anterior descending coronary artery (that is, collateral supply from septal branches of the right coronary artery or from other major coronary vessels may exist, a finding that could explain the false negative findings in Group C). (4) Recanalization of a previously obstructed proximal left anterior descending coronary artery may occur although residual scarring of the septum remains. (5) The septum may be distinctly myopathic as a result of factors other than large vessel coronary artery disease. Any number of these findings may have been the cause of discordance in the minority of our patients whose echocardiographic findings did not correlate with their angiographic findings.

Specificity of findings: Patients with idiopathic cardiomyopathy in the presence of normal coronary arteries may have abnormal septal motion on echocardiographic examination[12,13] or asynergy on left ventriculography.[31] In addition, these patients may have a chest pain syndrome. Thus, neither abnormal septal motion nor the associated abnormal PW/IVS ratio is specific for coronary artery disease and whether such data can be used to diagnose coronary artery disease must depend on the clinical setting in which they occur.

Left ventricular asynergy on ventriculography has been observed in approximately 60 percent of patients with obstructive lesions in the left anterior descending coronary artery defined as greater than 70 or 75 percent narrowing of the vessel lumen.[26–28] We detected left ventricular asynergy on standard echocardiography as manifested by either abnormal septal motion or an abnormal PW/IVS ratio, or both, in 15 of 19 patients with proximal left anterior descending coronary artery disease. No patient in our series with obstruction of less than 75 percent proximal to the first septal branch had echocardiographic evidence of septal asynergy. This finding lends further support to the widespread practice of defining hemodynamically significant ob-

structive coronary artery disease during the resting state as more than 75 percent narrowing of luminal diameter.

In conclusion, the findings of an abnormally decreased septal excursion and an abnormal posterior wall/interventricular septal excursion (PW/IVS) ratio are useful for detecting obstructive disease in the left anterior descending coronary artery when that obstruction is proximal to the first septal branch. A normal interventricular septal excursion and a normal PW/IVS ratio are usually found in patients without obstructive disease in the left anterior descending coronary artery or in patients with obstructive disease in this artery distal to the first septal branch. In addition, use of the ratio of PW/IVS excursion appears to be somewhat better than use of interventricular septal excursion alone in characterizing the location of left anterior descending disease.

Addendum

A recent report by Gordon and Kerber[32] presents results at variance with those of our study. We have no explanation for the disparate findings.

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Echocardiographic Observations in Opiate Addicts With Active Infective Endocarditis

Frequency of Involvement of the Various Valves and Comparison of Echocardiographic Features of Right- and Left-Sided Cardiac Valve Endocarditis

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Echocardiographic observations are described in 25 opiate addicts with active infective endocarditis involving apparently previously normal valves. Infective endocarditis was isolated to the tricuspid valve in 11 patients, involved both right- (tricuspid valve) and left-sided valves in 7 and was isolated to the left-sided valves in 7 (mitral valve in 6). Twenty patients (80 percent) had tricuspid valve regurgitation, 12 had mitral regurgitation, 3 had aortic regurgitation and none had pulmonary valve regurgitation. Considering the 75 cardiac valves (excluding the pulmonary) in the 25 patients, echocardiographic abnormalities consistent with active infective endocarditis were detected in 26 (74 percent) of the 35 clinically incompetent valves but in none of the 40 competent valves. Comparison of the 20 incompetent tricuspid valves with the 12 incompetent mitral valves indicated that (1) the echocardiogram was less sensitive in detecting tricuspid valve lesions, (2) rupture of tricuspid valve chordae tendineae was absent or not detectable, and (3) tricuspid valve vegetations tended to be larger.

Echocardiographic manifestations of cardiac valve vegetations were described for the first time in 1973.[1,2] Subsequently, other reports[3–10] confirmed and extended the initial observations. The following general conclusions from these studies appear justified: (1) there are echocardiographic features indicative of vegetations in many patients with active infective endocarditis, (2) these echocardiographic features occur mainly in the sickest patients, that is, those requiring valve replacement, and (3) the echocardiogram may be useful in the initial diagnosis of active infective endocarditis in patients with negative blood cultures.

The reported echocardiographic observations have mainly concerned patients with active infective endocarditis involving the left-sided cardiac valves: aortic in 33 patients and mitral in 25 patients.[1–10] To our knowledge, echocardiographic observations have been reported in only four patients with active infection involving a right-sided cardiac valve.[2,10] During a recent 19 month period, we studied with echocardiography 25 opiate addicts with active infective endocarditis. Because endocarditis in these patients usually involves previously normal valves, the resulting echocardiographic abnormalities can reasonably be attributed to the infective endocarditis rather than to a combination of underlying valve scarring plus superimposed valve infection. A high percent of patients have active infective endocarditis involving the tricuspid valve. This study describes the echocardiographic features in the 25 opiate addicts, focusing on the echocardiographic features produced by the tricuspid valve infection and comparing them with those produced by infection involving the mitral valve.

Material and Methods

Criteria for inclusion in this study included: (1) typical clinical features of active infective endocarditis (Table I); (2) regurgitation of at least one cardiac valve; (3) the recording of at least one echocardiogram during the period of active

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infective endocarditis; and (4) a history of recent opiate addiction (Table II). The 25 patients ranged in age from 21 to 49 years (average 29 years); 11 were women and 14 men. All were studied between October 1974 and May 1976 at either the District of Columbia General Hospital (17 patients) or the Howard University Hospital (8 patients). During this period, echocardiograms were obtained from all patients with active infective endocarditis whose presence was known to the cardiology staffs of either hospital.

Clinical diagnostic features (Tables I and II): All 25 patients had fever (more than 100° F), 22 had clinical evidence of pulmonary (17 patients) or systemic (3 patients) infarcts or both (2 patients) and all 25 had precordial murmurs of the regurgitant type.

Tricuspid regurgitation was diagnosed when a dominant *V* wave was observed in neck veins and when a blowing systolic murmur heard along the lower left sternal border increased in intensity with inspiration or leg raising, or both. Of the 20 patients with such a murmur, 18 also had clinical evidence of pulmonary infarction and these 18 were considered to have tricuspid regurgitation on the basis of infective endocarditis of the triscuspid valve; the remaining 2 patients (Cases 21 and 24) with a murmur of tricuspid regurgitation but no clinical evidence of pulmonary infarction were considered to have tricuspid regurgitation on a "functional" basis, that is, secondary to pulmonary hypertension from severe mitral regurgitation.

Mitral regurgitation was diagnosed when a blowing pansystolic murmur was heard loudest over the cardiac apex and with radiation into the left axilla. This murmur did not increase with inspiration and in addition was louder in intensity than the murmurs considered to represent tricuspid regurgitation. Twelve of the 25 patients were considered to have a murmur of mitral regurgitation: In 6 this was the only precordial murmur; the remaining 6 also had a murmur of tricuspid regurgitation, and 1 had a murmur of aortic regurgitation as well. Six of these 12 patients with mitral regurgitation

TABLE I

Clinical Observations in 25 Opiate Addicts With Active Infective Endocarditis

	Patients (no.)	
Positive blood cultures	24	
Fever (>100° F)	25	
Valve regurgitation	25	
Isolated right-sided	11	
Tricuspid (TV) only		11
Right- and left-sided	9*	
TV + mitral (MV)		7*
TV + aortic (AV)		1
TV + MV + AV		1
Isolated left-sided	7	
MV only		6
AV only		1
Emboli with infarcts	22	
Pulmonary (P)		17
Systemic (S)		3
P + S		2

* In two of these patients the murmur of tricuspid regurgitation was considered to be of functional origin secondary to pulmonary hypertension and not caused by infective endocarditis involving the tricuspid valve.

TABLE II

Clinical and Echocardiographic Observations in the 25 Opiate Patients With Active Infective Endocarditis

Case no.	Age (yr) & Sex	Regurgitant Murmur			Vegetation by Echo			Vegetation at Necropsy			Infecting Organism	Clinical Infarcts	
		TV	MV	AV	TV	MV	AV	TV	MV	AV		P	S
1	24M	+	0	0	+	0	0	+*	–	–	S aureus	+	0
2	26M	+	0	0	+	0	0	+	0	0	S aureus	+	0
3	34M	+	0	0	+	0	0	–	–	–	S aureus	+	+
4	28M	+	0	0	–	0	0	–	–	–	S aureus	+	0
5	45M	+	0	0	0	0	0	–	–	–	S aureus	+	0
6	29F	+	0	0	+	0	0	–	–	–	α-strep	+	0
7	21F	+	0	0	+	0	0	–	–	–	No growth	+	0
8	26F	+	0	0	0	0	0	–	–	–	S aureus	+	0
9	30M	+	0	0	–	0	0	–	–	–	S aureus	+	0
10	23M	+	0	0	0	0	0	–	–	–	S aureus	+	0
11	23F	+	0	0	+	0	0	–	–	–	S aureus	+	0
12	40M	+	+	0	+	0	0	–	–	–	S aureus	+	0
13	28F	+	+	0	+	+	0	–	–	–	S aureus	+	0
14	25F	+	+	0	+	+	0	–	–	–	S aureus	+	0
15	33F	+	+	0	+	+	0	–	–	–	S aureus	+	+
16	26M	+	+	0	+	+	0	–	–	–	S aureus	+	0
17	38F	+	0	+	+	0	+	–†	–†	–†	S aureus	+	0
18	27M	+	+	+	0	+	+	–†	–†	–†	Strep sp	+	0
19	23F	0	+	0	0	+	0	–	–	–	Enterococcus	0	0
20	24M	0	+	0	0	+	0	–	–	–	S aureus	0	+
21	36M	+‡	+	0	0	+	0	0	+	0	Enterococcus	0	+
22	29F	0	+	0	0	+	0	–	–	–	α-strep	0	0
23	21M	0	+	0	0	+	0	–	–	–	α-strep	0	0
24	25F	+‡	+	0	0	+	0	0	+	0	α-strep	0	+
25	49M	0	0	+	–	0	+	+§	0	+	S aureus	+	0

* Confirmed at time of cardiac operation. Patient alive.
† Died but no necropsy.
‡ Tricuspid regurgitation was mild and probably secondary to right ventricular systolic hypertension resulting from severe mitral regurgitation.
§ Vegetation small (<1 cm in diameter) and attached entirely to chordae tendinae of tricuspid valves, not to its leaflets.
AV = aortic valve; echo = echocardiography; MV = mitral valve; P = pulmonary; S = systemic; S aureus = Staphylococcus aureus; sp = species; strep = streptococcus; TV = tricuspid valve.
+ = present or positive; 0 = absent or negative; – = not applicable or no information available.

had clinical evidence of pulmonary infarction, and each of these 6 also had a murmur of tricuspid regurgitation that was attributable to infective endocarditis involving the tricuspid valve. Of the remaining six patients with a murmur of mitral regurgitation but no pulmonary infarct, four had only this murmur; the other two also had a murmur of tricuspid regurgitation that was considered of functional origin because neither patient had pulmonary infarcts or echocardiographic evidence of vegetations on the tricuspid valve leaflets.

Aortic regurgitation was diagnosed in three patients (Cases 17, 18 and 25) on the basis of a diastolic blowing murmur over the base of the heart or along the left sternal border. The

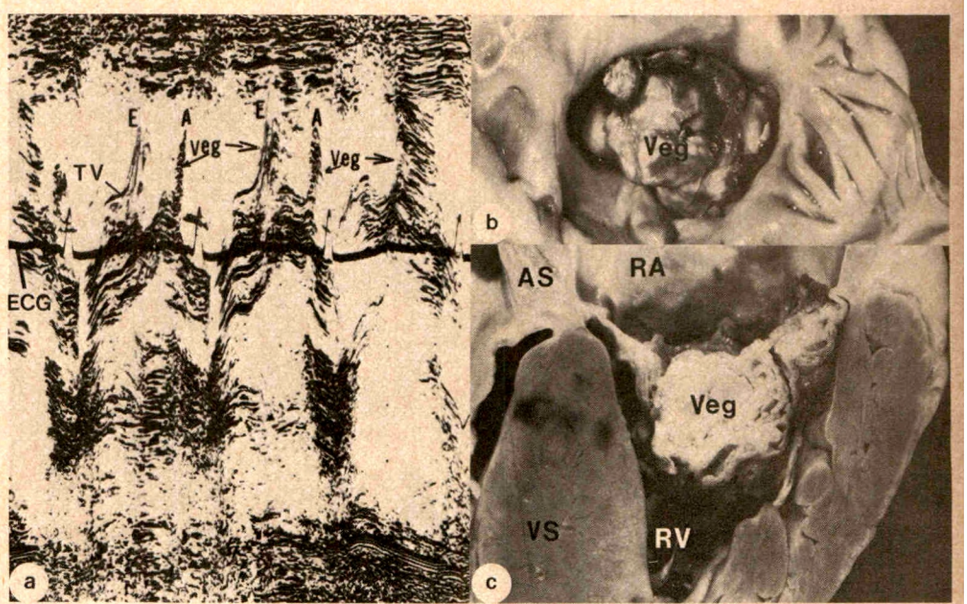


FIGURE 1. Case 2. This man had clinical signs and symptoms of active infective endocarditis for about 84 days. This echocardiogram **(a)** was recorded 5 days before death. Masses of echoes (veg) fill most of the space encompassed by the tricuspid valve (TV) leaflets in diastole. The E and A points of the tricuspid valve echoes are shown. **b,** the tricuspid valve orifice, as viewed from the right atrium, is completely occupied by vegetation (veg). **c,** longitudinal section of heart showing the space between the tricuspid valve leaflets completely occupied by vegetative material. AS = atrial septum; ECG = electrocardiogram; RA = right atrium; RV = right ventricle; VS = ventricular septum.

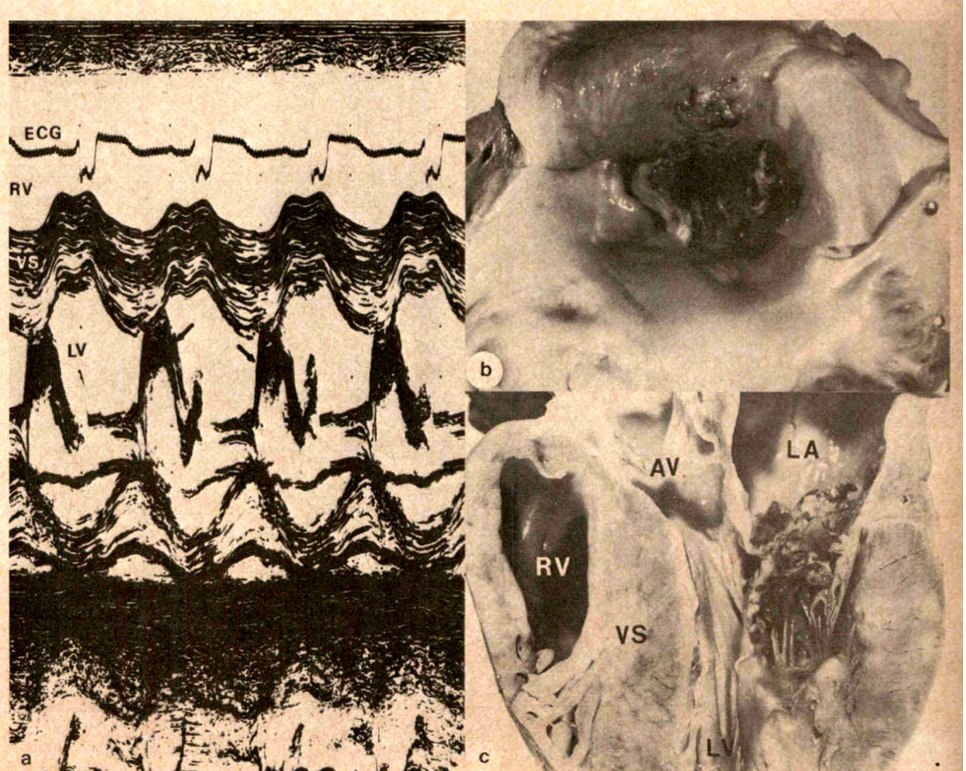


FIGURE 2. Case 21. This man had clinical signs and symptoms of active infective endocarditis for about 30 days. **a,** echocardiogram recorded 7 days before death showing marked thickening of the mitral leaflets **(arrows).** The motion of the ventricular septum (VS), posterior left ventricular (LV) wall and anterior mitral leaflet is exaggerated. Prolapse of the mitral valve leaflet into the left atrium also was recorded (not shown). The right ventricle (RV) is dilated. A small posterior echo-free space indicating pericardial effusion also is present. **b,** view of mitral valve as seen from the left atrium. A tongue of the anterior mitral leaflet protrudes into this cavity and a jet lesion is present on the left atrial wall. **c,** longitudinal view of the heart showing prolapse of a portion of the anterior mitral valve leaflet into the left atrium (LA). The tongue of the prolapsed anterior leaflet contacts the mural endocardium of the left atrium at the site of the jet lesion. Although the ventricular septum appears to be thicker than the ventricular free wall, the cut of the septum is not completely perpendicular to it. Other cuts showed the septum to be no thicker than the left ventricular free wall. AV = aortic valve; ECG = electrocardiogram.

murmur was considered of aortic rather than of pulmonary valve origin because each of the three patients had a cuff diastolic blood pressure of less than 60 mm Hg, bounding systemic arterial pulses and echocardiographic evidence of vegetations on the aortic valve cusps. Pulmonary valve regurgitation was not diagnosed clinically (or with echocardiography) in any of the 25 patients.

Sites of valve vegetations: Determination of these sites was based on the presence of precordial murmurs typical of regurgitation involving one or more of the various cardiac valves (Table I). Eighteen patients had a murmur typical of regurgitation of only one valve: tricuspid in 11, mitral in 6 and aortic in 1; the other 7 had murmurs indicative of regurgitation of more than one valve. Seven patients had evidence of regurgitation limited to a left-sided cardiac valve; only one of these (Case 25) had pulmonary changes compatible with infarction and, at necropsy, this patient was found to have a small vegetation on the chordae tendineae of the tricuspid valve in

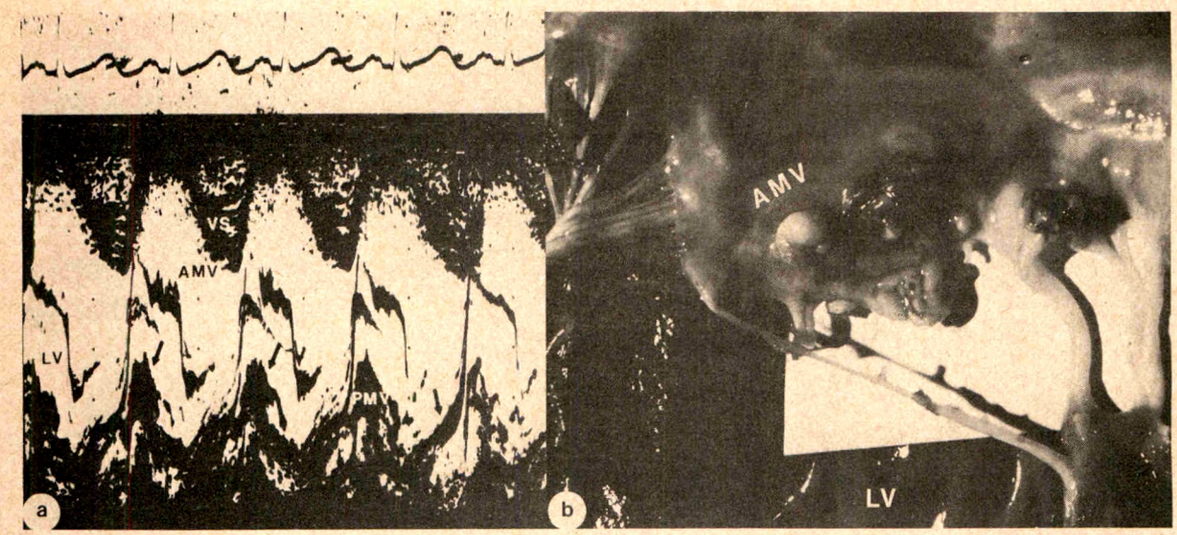


FIGURE 3. Case 24. This woman had signs and symptoms typical of active infective endocarditis for 60 days before death. **a,** echocardiogram recorded 3 days before death showing irregular thickening **(arrows)** of the mitral valve leaflets and erratic opening motion of the anterior mitral leaflet (AMV). The posterior mitral leaflet (PMV) moves anteriorly in early diastole and slightly posteriorly in early systole. Motion of the ventricular septum (VS) is greatly exaggerated. These changes are compatible with rupture of mitral chordae tendineae due to active infective endocarditis. **b,** opened mitral valve showing a vegetation on the atrial aspect of the posterior half of the anterior leaflet. Most of the chordae have ruptured at this site. LV = left ventricle.

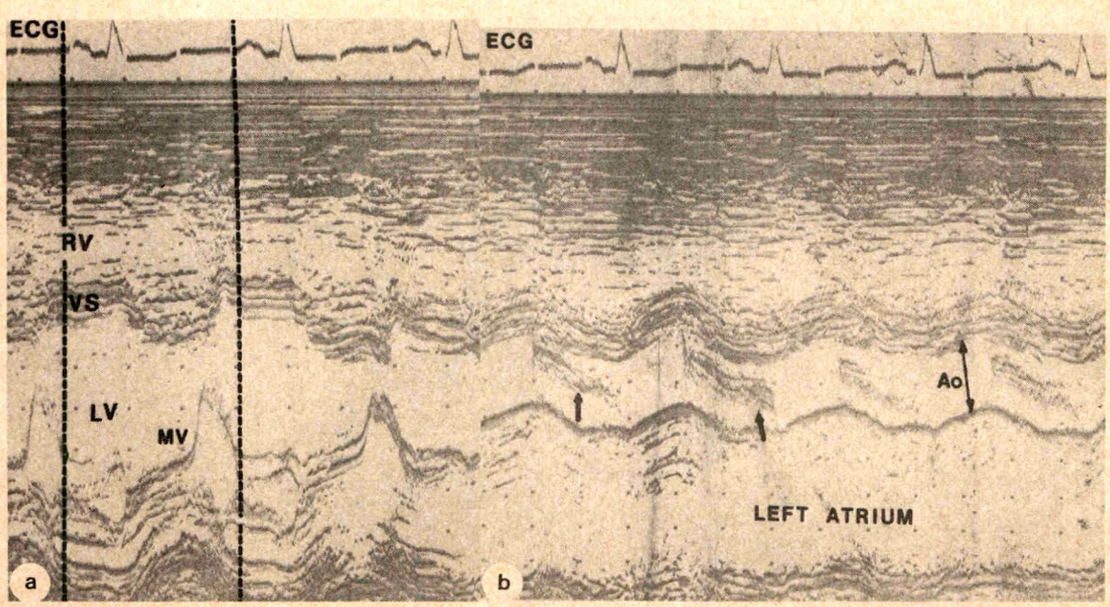


FIGURE 4. Case 17. Echocardiogram obtained 2 days before death. Clinically, the patient had evidence of both severe tricuspid and severe aortic valve regurgitation. **a,** there is diastolic fluttering of the mitral leaflets. **b,** fine diastolic fluttering **(arrows)** of aortic valve cusps, thickened presumably by vegetative material. The fluttering of these cusps and the premature closure of the mitral leaflets, which developed 2 days before death, are indicative of aortic valve cuspal perforation or tear, or both. Ao = aorta; ECG = electrocardiogram; LV = left ventricle; MV = mitral valve; RV = right ventricle; VS = ventricular septum.

addition to vegetations on the aortic valve. The other 18 patients had evidence of tricuspid valve regurgitation that was isolated in 11 and associated with left-sided regurgitation in the other 7; all 18 had radiographic changes consistent with pulmonary infarction, presumably secondary to dislodgment of vegetative material from the tricuspid valve. None of the 25 patients had historical or recorded evidence of a precordial murmur before the onset of active infective endocarditis, and none had a history of rheumatic fever or clinical evidence of valve stenosis.

Necropsy findings (Table II): Six of the 25 patients died from consequences of the active infective endocarditis, and necropsy was performed in 4; an additional patient (Case 1) underwent successful operative excision of the tricuspid valve. The other 18 patients recovered and were discharged from the hospital. Studies at necropsy or operation confirmed that the clinical diagnosis of involvement of one or more valves by the infective process was correct in all five patients so examined. In Case 25, however, necropsy disclosed a single small vegetation on several chordae tendineae of the tricuspid valve although evidence of tricuspid valve dysfunction had not occurred during life. In Case 1 cardiac operation confirmed that each of the tricuspid valve leaflets had large vegetations that appeared to prevent proper coaptation of the leaflets during ventricular systole. The tricuspid valve anulus was dilated. In Case 2 necropsy disclosed huge vegetations on each of the three tricuspid valve cusps. In Case 25, a single large vegetation on the aortic valve at the junction of the right and noncoronary cusps caused detachment of both of these cusps at, and adjacent to, their commissural attachment. The detachment resulted in severe aortic regurgitation. In addition, the aortic vegetation extended through the membraneous ventricular system to appear on the right side of the heart on the underside of the junction of the septal and anterior tricuspid valve leaflets. As mentioned earlier, a small vegetation encircled several chordae tendineae attached to the tricuspid valve leaflets.

Echocardiograms: A total of 55 echocardiograms were recorded in the 25 patients. Tracings are illustrated from three of the five patients whose sites of cardiac valve vegetations were confirmed morphologically (Fig. 1 to 3) and from two additional patients with echocardiographic confirmation of vegetations on each of two cardiac valves (Fig. 4 and 5).

Two types of echocardiographic recorders were used: (1) a Unirad 100 series (D.C. General) or (2) a Honeywell 1856 strip-chart recorder (Howard). Each machine utilized a 0.5 inch (1.27 cm) diameter, 2.25 megahertz transducer with a repetitive rate of 1,000 pulses/sec. Recordings were made in the standard fashion[11] with the patient supine at an inclination of 45°. Each valve studied was continuously scanned. Echocardiographic criteria utilized as indicative of lesions resulting from active infective endocarditis are defined in Table III.[1–10,12,13]

TABLE III

Echocardiographic Characteristics of Cardiac Valve Lesions Resulting From Active Infective Endocarditis

Anatomic Lesion	Applicable Cardiac Valve	Echocardiographic Characteristics
1. Valve vegetations	TV, MV, AV	Irregular ("shaggy") thickening of valve echoes
2. Torn or perforated valve cusp	TV	Uncertain
	MV	Uncertain
	AV	Fine diastolic "fluttering" of the cusps; diastolic separation of the cusps; prolapse of cusp into left ventricular outflow tract
3. Ruptured chordae tendineae	TV, MV	Atrioventricular valve echoes in the atria; coarse, erratic diastolic opening movements of anterior leaflet (either TV or MV); prolapse of atrioventricular leaflet(s); diastolic thickenings of the valvular leaflets
4. Ring abscess	TV, MV, AV	Uncertain

AV = aortic valve; MV = mitral valve; TV = tricuspid valve.

Results

Four valve lesions occurring during active infective endocarditis are recognized:[14–17] (1) vegetations; (2)

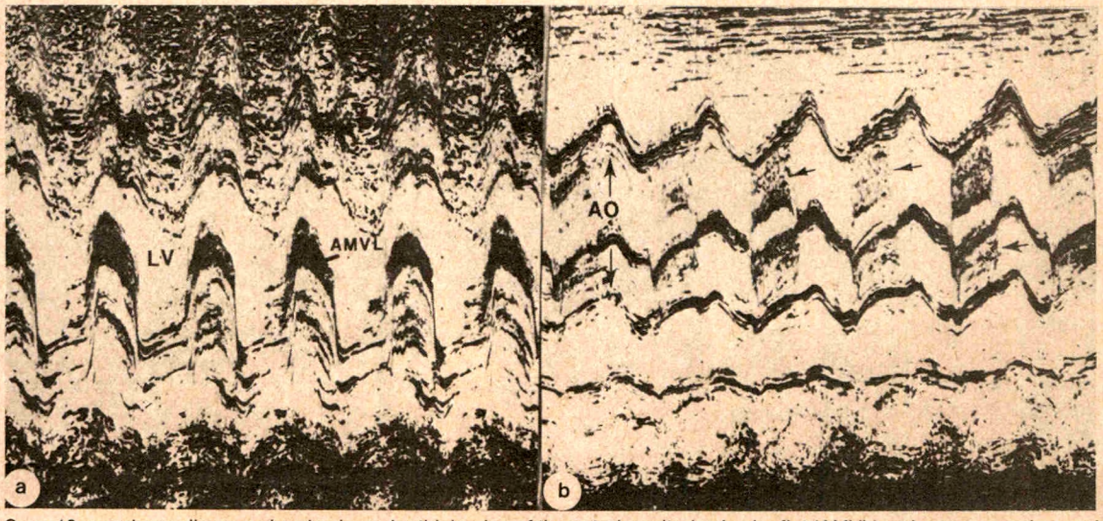


FIGURE 5. Case 18. **a,** echocardiogram showing irregular thickening of the anterior mitral valve leaflet (AMVL) and coarse erratic opening motion of the mitral leaflets. The motion of the ventricular septum is exaggerated. **b,** there are masses of echoes **(arrows)** on the aortic valve cusps. AO = aorta; LV = left ventricle.

TABLE IV

Frequency of Echocardiographic Detection of Cardiac Valve Lesions of Active Infective Endocarditis (IE) in 25 Opiate Addicts

	Valves (no.)	Valves Adequately Seen by Echo (no.)	Valve by Echo	
			Abnormal (no.)	Normal (no.)
Tricuspid	20	18	12	6
Vegetation		18	12	–
Torn or perforated cusp		18	0	–
Ruptured chordae tendineae		18	0	–
Ring abscess		18	0	–
Mitral	12	12	11	1
Vegetation		12	11	–
Torn or perforated cusp		12	0	–
Ruptured chordae tendineae		12	3	–
Ring abscess		12	0	–
Aortic	3	3	3	0
Vegetation		3	3	–
Torn or perforated cusp		3	2	–
Ruptured chordae tendineae		–	–	–
Ring abscess		3	0	–
Totals	35	33	26	7

cuspal tears or perforations; (3) ruptured chordae tendineae, and (4) ring abscess. The number of valves in the 25 patients with echocardiographic demonstration of these four lesions are summarized in Table IV.

The mitral and aortic valves were well visualized with the echocardiogram in all 25 patients and the tricuspid valve was well seen in 22 (Table II). Echocardiograms disclosed lesions indicative of active infective endocarditis in one valve (14 patients) or two or three valves (6 patients) in 20 of the 25 patients (80 percent). No valve lesions were evident in five patients (20 percent) (Fig. 1 to 5). However, in each of these five patients, the infective endocarditis clinically was limited to the tricuspid valve, and in two of these the tricuspid valve leaflets were not recorded at all in the echocardiogram. Auscultatory evidence of regurgitation in one valve (16 patients) or more (9 patients) was present in all 25 patients. Of all 75 valves (excluding the pulmonary valves) in the 25 patients, 35 were incompetent and 40 were functionally normal. Of the 35 incompetent valves, 33 were adequately visualized with the echocardiogram; in 26 (79 percent) of these 33 cases, the echocardiogram disclosed lesions indicative of active infective endocarditis; in the remaining 7 (21 percent) findings were normal (Table IV). Of the 20 incompetent tricuspid valves, 18 were adequately visualized with the echocardiogram, which disclosed lesions consistent with active infective endocarditis in 12 (67 percent) and showed normal findings in 6 (33 percent). There were 12 clinically incompetent mitral valves; in 11 cases (92 percent) the echocardiogram disclosed valve lesions indicative of active infective endocarditis and no valve lesions in the remaining case (8 percent) (Table IV). In all three cases of aortic valve regurgitation, the echocardiogram revealed valve lesions indicative of active infective endocarditis.

In none of the 25 patients nor in any of the 75 valves (pulmonary valve excluded) were valve lesions indicative of underlying disease detected with the echocardiogram, and none of the five patients with morphologic confirmation had underlying valve disease.

Comments

Previous necropsy studies of patients with right-sided active infective endocarditis[14,17,18] and of opiate addicts with either left- or right-sided infective endocarditis have shown that the involved valves were nearly always anatomically normal before the onset of the cardiac infection.[17,19] All 25 patients in our study were opiate addicts, none had documented evidence of a precordial murmur before the onset of infective endocarditis and none had a history of rheumatic fever; of the 5 patients studied at necropsy (4 patients) or at cardiac operation (1 patient), none had evidence of previous or chronic cardiac valve disease. Thus, it is reasonable to believe that the active infective endocarditis in our 25 patients involved previously normal valves and that the changes observed in their echocardiograms are attributable to infective endocarditis. In our 25 patients, all 40 competent valves (excluding the pulmonary valve) were normal on echocardiography and echocardiographic abnormalities consistent with infective endocarditis were detected in 26 (74 percent) of the 35 incompetent valves.

Tricuspid versus mitral regurgitant valves: Comparison of the 20 regurgitant tricuspid valves in our 25 patients with the 12 regurgitant mitral valves disclosed several differences: (1) The echocardiogram was less sensitive in detecting lesions resulting from infective endocarditis in the tricuspid than in the mitral valve; (2) the echocardiogram detected on the tricuspid valve only one of the four recognized valve lesions (Table IV) resulting from active infective endocarditis (vegetations), whereas it detected both vegetations and ruptured chordae tendineae on the mitral valve; (3) the vegetations detected with echocardiography on the tricuspid valve generally appeared larger than those detected on the mitral valve.

Aortic regurgitant valves: Although it does not appear appropriate to compare atrioventricular with semilunar valves, two of our three patients with an incompetent aortic valve secondary to active infective endocarditis had echocardiographic evidence of torn or perforated cusps, whereas none of the 20 patients with an incompetent tricuspid valve had such evidence. This difference is understandable in view of necropsy studies showing the infrequency of tears or perforations in the tricuspid valve leaflets and the frequency of these lesions in the aortic valve cusps.[17]

Our 25 opiate addicts with active infective endocarditis had unusually infrequent evidence of aortic regurgitation. Only 3 of the 35 valves with clinical evidence of regurgitation were aortic. Previous echocardiographic studies[1–10] and a recent necropsy study[17]

showed that the aortic valve was the valve most frequently involved in active infective endocarditis.

Accuracy of echocardiographic diagnosis: Among the 20 clinically recognized incompetent tricuspid valves in our 25 patients, 18 had adequate echocardiographic visualization of the tricuspid valve leaflets and only 12 of these (67 percent) showed echocardiographic abnormalities indicative of active infective endocarditis. In contrast, echocardiographic features indicative of active infective endocarditis were recognized in 11 (92 percent) of 12 incompetent mitral valves and in 3 of 3 incompetent aortic valves.

Tricuspid versus mitral valve vegetations and chordal rupture: Necropsy studies[14,15,17] have demonstrated that vegetations on the tricuspid valve tend to be larger than those on other valves, and in our 25 patients the largest vegetations assessed with echocardiography were located on the tricuspid valve. The explanation for this observation is uncertain. The average anular circumference of the tricuspid valve is larger than that of the mitral valve (11 versus 9 cm); therefore, a tricuspid valve vegetation has a larger area within which to grow. The smaller systolic pressure in the right ventricle (compared with the left ventricle) may also be a factor. Rupture of tricuspid valve chords is infrequent, whereas mitral chordal rupture in infective endocarditis is frequent. The greater incidence of chordal rupture with mitral infection may be due to the greater left ventricular systolic pressure. The infrequency of chordal rupture on the tricuspid valve may delay development of significant tricuspid regurgitation and allow the right-sided vegetations to grow larger before valve dysfunction ensues.

To our knowledge, no echocardiographic investigation has detected the occurrence of a valve ring abscess from active (or healed) infective endocarditis. However, these abscesses rarely involve the tricuspid valve and occur frequently only in patients with infective endocarditis involving the aortic valve[16]; only 3 of our 25 patients had infection involving the aortic valve.

Pulmonary valve involvement: In none of our 25 patients and in none reported has echocardiography detected lesions of active infective endocarditis on the pulmonary valve. The echocardiogram of the pulmonary valve was recorded in 12 of our patients. Only 3 of the 25 patients, however, had auscultatory evidence of regurgitation in a semilunar valve and in each it was clear that aortic rather than pulmonary valve regurgitation was present. Furthermore, infection of a pulmonary valve is extremely rare except in patients with congenital heart disease; in previous studies of opiate addicts studied at necropsy,[17,18] involvement of the tricuspid valve by vegetation was more than 10 times as common as involvement of the pulmonary valve.

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Mode of Initiation of Reciprocating Tachycardia During Programmed Ventricular Stimulation in the Wolff-Parkinson-White Syndrome

With Reference to Various Patterns of Ventriculoatrial Conduction

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The mode of initiation of reciprocating tachycardia in relation to various patterns of ventriculoatrial (V-A) conduction induced by programmed right ventricular stimulation was systematically analyzed in 29 patients with the Wolff-Parkinson-White (WPW) syndrome, type A. His bundle activity and atrial electrograms near the atrial ends of the normal and accessory pathways were simultaneously recorded. V-A conduction time was plotted as a function of premature ventricular coupling intervals. Four groups of patients were observed. In Group I, four patients with absence of V-A conduction, reciprocating tachycardia could not be elicited. In Group II, three patients with persistent retrograde atrial fusion from the normal and accessory pathways, reciprocating tachycardia could not be elicited because of a constant impulse collision at the atrial level. In Group III, seven patients with predominant or exclusive V-A conduction over the normal pathway, concealed retrograde penetration of the accessory pathway might have prevented the initiation of reciprocating tachycardia in all patients. In Group IV, 15 patients with predominant or exclusive V-A conduction over the accessory pathway, reciprocating tachycardia could be elicited only in 7, and its initiation appeared to depend upon the depth of retrograde penetration of the normal pathway; the less the depth of such penetration, the easier it was to elicit a reciprocating tachycardia. Furthermore, with the production of progressively less deep retrograde penetration of the normal pathway, development of repetitive ventricular responses at short ventricular coupling intervals and shortening of the ventricular driving cycle length favored the induction of reciprocating tachycardia in patients in this group. The study demonstrates that the initiation of reciprocating tachycardia during programmed ventricular stimulation in patients with the WPW syndrome is related to various patterns of V-A conduction.

Wellens and Durrer[1] suggested that various patterns of ventriculoatrial (V-A) conduction could be induced by programmed ventricular stimulation in patients with the Wolff-Parkinson-White (WPW) syndrome. This hypothesis was based on the existence of different electrophysiologic properties of the two anatomically separate atrioventricular (A-V) pathways—the A-V node-, His-, Purkinje system (normal pathway) and the Kent bundle (accessory pathway). By recording atrial electrograms near the atrial ends of these two pathways, Svenson et al.[2] subsequently corroborated this hypothesis by measuring V-A conduction time as a function of increasing prematurity of a ventricular extrasystole. In this study in patients with the WPW syndrome, type A we analyzed systematically the mode of induction of reciprocating tachycardia in relation to various patterns of V-A conduction elicited by programmed right ventricular stimulation.

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Materials and Methods

Patients: The study population comprised 29 patients with the WPW syndrome, type A who had high right atrial, low septal right atrial and left atrial electrograms recorded simultaneously during electrophysiologic studies. There were 12 male and 17 female patients ranging in age from 14 to 65 (mean 32.4) years. Clinically all patients experienced paroxysmal episodes of palpitations. Twenty-five had at least one episode of tachycardia documented electrocardiographically—supraventricular tachycardia in 21 and atrial flutter-fibrillation in the other 4. All patients gave informed consent to the study. At the time of study, no patient was receiving digitalis or any antiarrhythmic drug.

Recordings: The study was performed with the patients in a postabsorptive nonsedated state. High right atrial activity was recorded through the proximal pair of electrodes of a hexapolar electrode catheter (Berkovits-Castellanos, USCI no. 003932, 6F) and the left atrial electrogram was recorded with a quadripolar electrode catheter (USCI no. 002943, 6F) placed in the coronary sinus in all patients except one whose left atrium was entered through a patent foramen ovale (Fig. 1). With use of a conventional technique,[3] the His bundle electrogram was recorded through a tripolar electrode catheter (Castillo, Elecath no. 07315, 5F), from which low septal right atrial activity was recorded as well. The interelectrode distances for recording were 1 cm. The intracardic bipolar electrograms were then displayed simultaneously with standard surface electrocardiographic leads I, II and V_1 on a multichannel oscilloscopic photographic recorder (Electronics for Medicine, DR-16), at a paper speed of 100 mm/sec, using a filter setting between 40 and 500 hertz.

Programmed right ventricular stimulation: Through the remaining pairs of electrodes of the hexapolar and quadripolar electrode catheters, both the atria and the right ventricular apical endocardium were stimulated at two or more cycle lengths (A_1-A_1 or V_1-V_1) with use of a programmed digital stimulator that delivered stimuli (S_1 and S_2) with a duration of 2.0 msec at approximately twice diastolic threshold. After every eighth spontaneous or paced beat (A_1 or V_1), single premature atrial or ventricular beats (A_2 or V_2) were delivered at progressively shorter coupling intervals until the effective refractory period of the atrium or ventricle was encountered.

The following observations[4–6] suggested the presence of a left-sided accessory pathway in each patient: (1) Programmed left atrial stimulation induced a tall R wave in lead V_1 during maximal ventricular preexcitation; or (2) the sequence of retrograde atrial activation during reciprocating tachycardia or induced by programmed ventricular stimulation indicated that left atrial activation preceded low septal right atrial activation (in the His bundle electrographic lead) and high right atrial activation.

The effective refractory period of the accessory pathway was measured using recording sites close to the location of the pathway.[2,7] The antegrade and retrograde effective refractory periods of the accessory pathway were defined as the longest A_1-A_2 or V_1-V_2 intervals, respectively, near the accessory pathway that failed to propagate over it. With the method described by Svenson et al.,[2] V-A conduction time (the V_2-A_2 interval) was plotted as a function of the premature ventricular coupling interval (V_1-V_2). The initiation of reciprocating tachycardia relative to various patterns of V-A conduction was then systematically studied and reviewed.

Results

Patterns of V-A Conduction

As suggested by several investigators,[1,2,8–11] retrograde conduction over the normal pathway differs from that over the accessory pathway. In response to increasing prematurity of a ventricular extrasystole, retrograde conduction time over the normal pathway gradually lengthens, whereas it remains relatively constant over the accessory pathway. Therefore, various patterns of V-A conduction induced by programmed

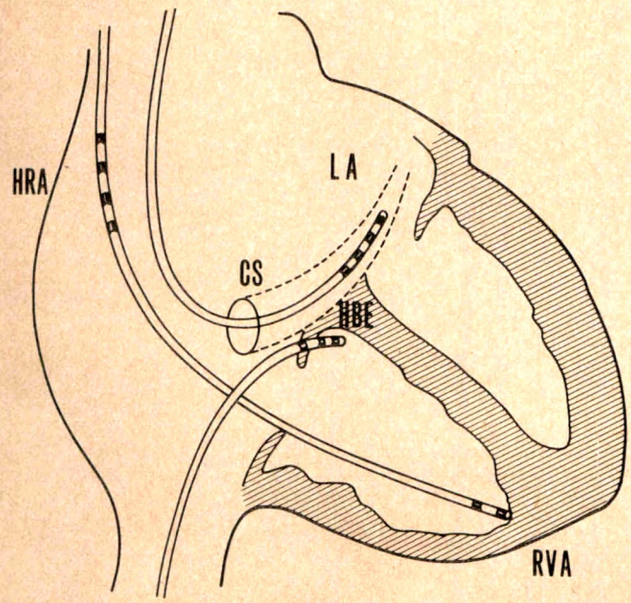


FIGURE 1. Catheter electrode positions used for intracardiac recording and stimulation. CS = coronary sinus; HBE = His bundle electrographic lead (recording His bundle and low septal right atrial electrograms); HRA = high right atrium; LA = left atrium; RVA = right ventricular apex.

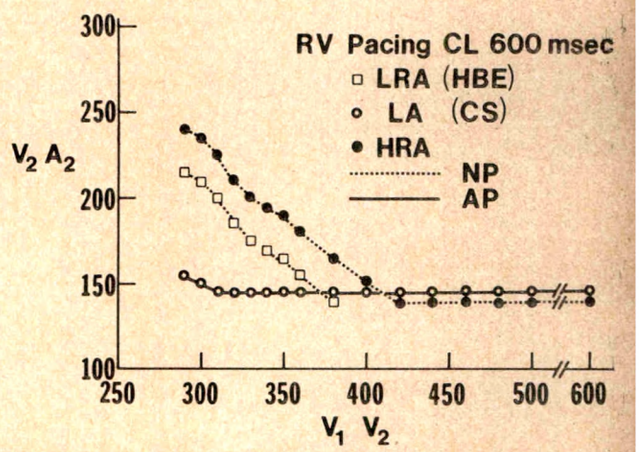


FIGURE 2. Retrograde conduction time of premature ventricular beats (V_2-A_2) as a function of premature coupling intervals (V_1-V_2) in a patient with a left-sided accessory pathway (AP). Persistent retrograde atrial fusion from the accessory pathway and normal (NP) pathway is evident. Retrograde atrial activation time remains relatively unchanged in the left atrium (LA), whereas it lengthens 100 msec in the high right atrium (HRA) at the V_1-V_2 interval of 290 msec. No reciprocating tachycardia can be elicited. CL = cycle length; CS = coronary sinus; HBE = His bundle electrographic lead; LRA = low septal right atrium; RV = right ventricular.

ventricular stimulation can theoretically be differentiated. According to these patterns of V-A conduction, four groups of patients (I, II, III and IV) were observed, and the modes of initiation of reciprocating tachycardia in relation to these various patterns of V-A conduction were as follows:

Group I: Absence of V-A conduction due to retrograde block in both normal and accessory pathways (four patients): The sequence of atrial activation during programmed ventricular stimulation in these four patients was the same as that of sinus nodal activity; the high right atrium was activated before the low septal right atrium near the normal pathway (in the His bundle electrographic lead) and the left atrium. Because the atrial rate was constantly slower than the basic ventricular pacing rate (A_1-A_1 longer than V_1-V_1), retrograde block in both pathways allowing independent sinus nodal activity to emerge was responsible for this sequence. Reciprocating tachycardia could not be elicited by programmed stimulation from either the atria or the right ventricle, and no reciprocating tachycardia was ever documented clinically in these four patients. Similar observations have been reported by Wellens and Durrer.[1]

Group II: Persistent retrograde atrial fusion secondary to conduction wave fronts from the normal and accessory pathways (three patients): In these three patients, retrograde low septal right atrial and high right atrial activation times (V_2-LRA_2 and V_2-HRA_2 intervals) gradually lengthened, whereas retrograde left atrial activation time (V_2-LA_2 interval) remained relatively constant as the premature ventricular coupling interval (V_1-V_2) shortened (Fig. 2). These findings suggested that (1) both the low septal right atrium and the high right atrium were activated in retrograde manner from the normal pathway; (2) the left atrium was activated in retrograde manner from the accessory pathway, resulting in retrograde atrial fusion; and (3) the retrograde effective refractory periods of the two pathways were almost identical.[1,2] Reciprocating tachycardia could not be elicited with programmed ventricular stimulation in these three patients.

Group III: Predominant or exclusive retrograde atrial activation from the normal pathway (seven patients): Three of the seven patients had a V-A conduction pattern suggestive of a shift from retrograde atrial fusion to exclusive retrograde atrial activation

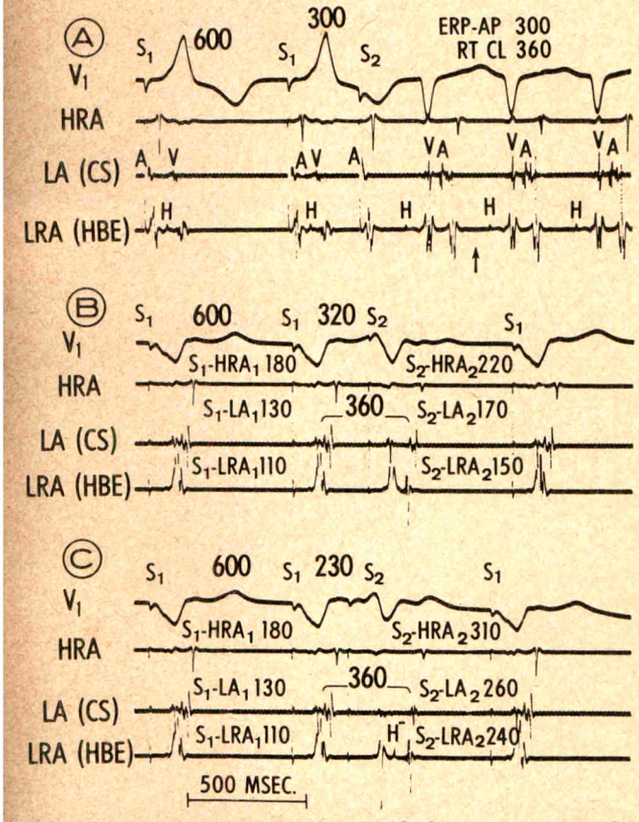


FIGURE 3. A, during left atrial (LA) pacing (S_1-S_1) at a cycle length (CL) of 600 msec, a premature atrial coupling interval (S_1-S_2) of 300 msec results in the disappearance of ventricular preexcitation and initiates reciprocating tachycardia (RT) **(arrow)**. Therefore, the antegrade effective refractory period (ERP) of the accessory pathway (AP) is 300 msec (LA_1-LA_2 = S_1-S_2). The tall R wave in lead V_1 during left atrial pacing and the sequence of atrial activation during reciprocating tachycardia suggest that the accessory pathway is left-sided. **B** and **C,** during right ventricular pacing (S_1-S_1) at a cycle length of 600 msec, there is progressive lengthening of V-A conduction time at all three atrial recording sites (low septal right atrium, LRA; left atrium, LA; and high right atrium, HRA) in response to increasing prematurity of ventricular coupling intervals (S_1-S_2). The low septal right atrium (in His bundle electrographic lead, HBE) is constantly activated 20 and 70 msec before the left atrium and high right atrium, respectively, suggestive of retrograde conduction over the normal pathway. Note LA_1-LA_2 intervals at S_1-S_2 of both 320 and 230 msec are 360 msec, which is beyond the antegrade effective refractory period of the accessory pathway at a comparable cycle length of 600 msec; however, no reciprocating tachycardia is elicited. H^- = retrograde His bundle potential. Electrocardiographic leads I and II are deleted in this and subsequent figures. CS = coronary sinus.

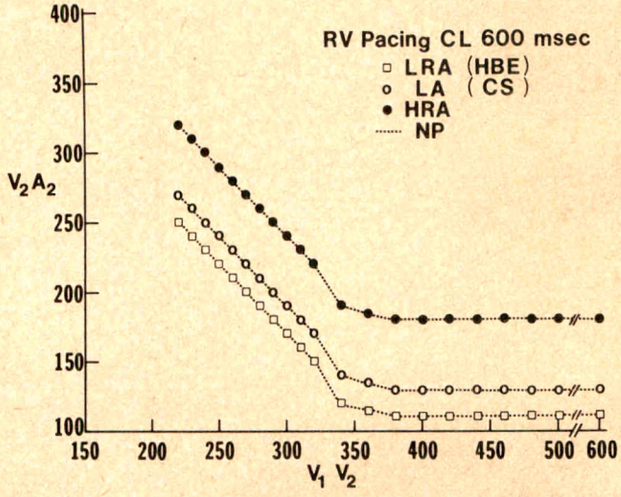


FIGURE 4. Same patient. Retrograde conduction time of premature ventricular beats (V_2-A_2) as a function of premature coupling intervals (V_1-V_2), demonstrating exclusive ventriculoatrial conduction from the normal pathway (NP). Note the progressive lengthening of retrograde atrial activation time in three atrial recording sites (high right atrium, HRA; left atrium, LA; low septal right atrium, LRA). CL = cycle length; CS = coronary sinus; HBE = His bundle electrographic lead; RV = right ventricular.

from the normal pathway as the premature ventricular coupling interval (V_1-V_2) shortened, owing to the retrograde effective refractory period of the accessory pathway being longer than that of the normal pathway.[1,2] In the remaining four patients, retrograde atrial activation was exclusively from the normal pathway throughout the premature ventricular coupling intervals (V_1-V_2). Although reciprocating tachycardia could be induced during programmed atrial stimulation, it could not be elicited with programmed ventricular stimulation in these seven patients.

One example is shown in Figures 3 and 4. During left atrial pacing at a driving cycle length of 600 msec, the longest atrial coupling interval (LA_1-LA_2) that failed to conduct over the accessory pathway was 300 msec (antegrade effective refractory period of the accessory pathway), and a reciprocating tachycardia was elicited (Fig. 3A). The tall R waves in lead V_1 during left atrial pacing and the sequence of retrograde atrial activation during reciprocating tachycardia in which the left

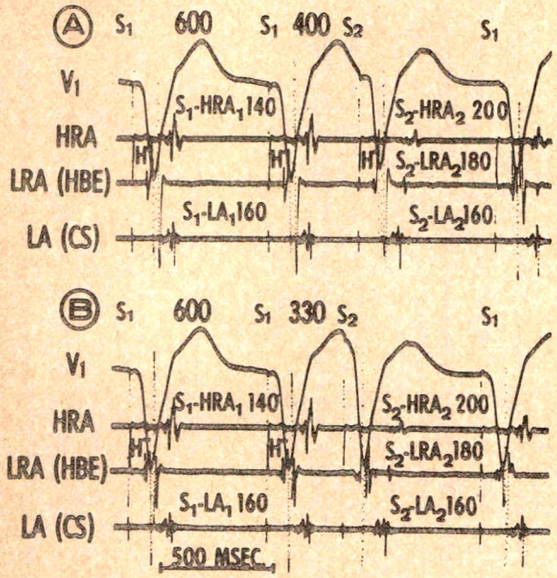


FIGURE 5. During right ventricular pacing (S_1-S_1) at a cycle length of 600 msec, high right atrial (HRA) activation precedes left atrial (LA) activation by 20 msec (S_1-HRA_1 = 140 msec, S_1-LA_1 = 160 msec). However, when the premature coupling interval (S_1-S_2) is shortened to 400 msec **(A)** or less **(B)**, the low septal right atrial (LRA) electrogram (in the His bundle electrographic lead, HBE) becomes discernible. The sequence of atrial activation then reveals that the left atrium was constantly activated 20 and 40 msec, respectively, before the low septal right atrium and the high right atrium, suggestive of a shift in the pattern of ventriculoatrial conduction from retrograde atrial fusion to the one of exclusive retrograde atrial activation from the accessory pathway. CS = coronary sinus.

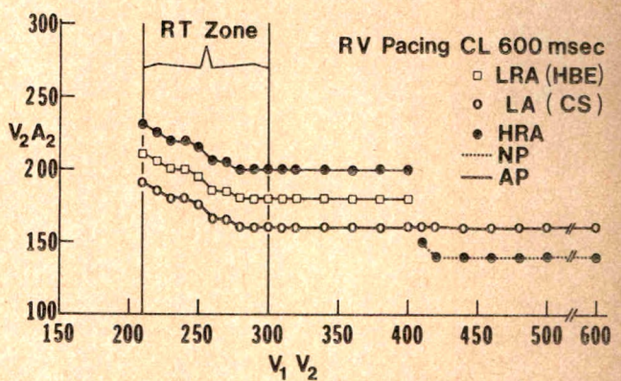


FIGURE 6. Same patient. Retrograde conduction time of premature ventricular beats (V_2-A_2) as a function of premature coupling intervals (V_1-V_2), demonstrating a shift of the ventriculoatrial conduction pattern from retrograde atrial fusion to exclusive retrograde atrial activation from the accessory pathway (AP). A reciprocating tachycardia (RT) zone is defined between premature coupling intervals (V_1-V_2) of 300 and 210 msec and, in each instance, the onset of reciprocating tachycardia is related to repetitive ventricular responses (see Fig. 7). CL = cycle length; CS = coronary sinus; HBE = His bundle electrographic lead; HRA = high right atrium; LA = left atrium; LRA = low septal right atrium; NP = normal pathway; RV = right ventricular.

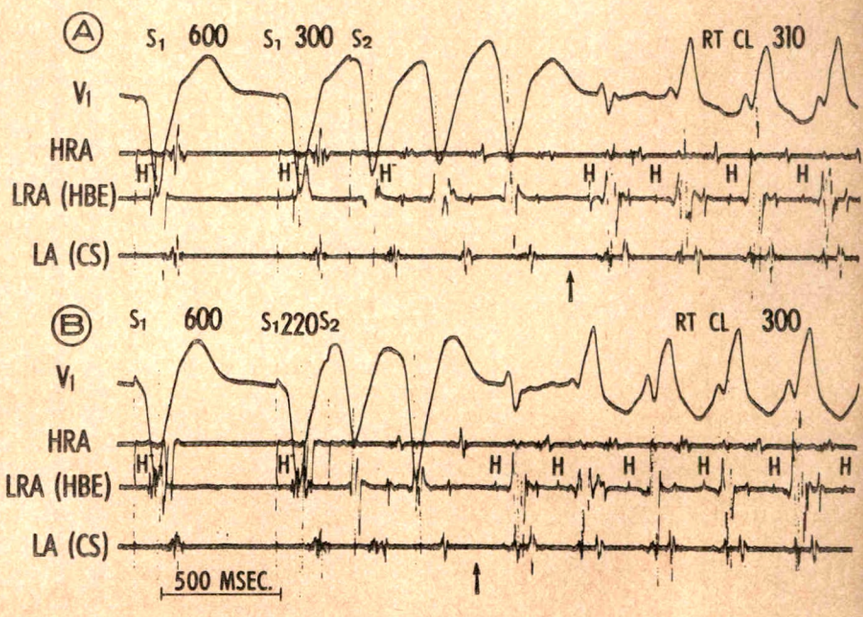


FIGURE 7. Same patient. During right ventricular pacing (S_1-S_1) at a cycle length (CL) of 600 msec, repetitive ventricular responses ($V_2V_3V_4$ in **A** or V_2V_3 in **B**) at short premature coupling intervals (S_1-S_2) initiate an onset of reciprocating tachycardia (RT) **(arrows)**. Note persistent retrograde atrial activation from the accessory pathway (AP) during repetitive ventricular responses and the development of a functional complete right bundle branch block pattern during reciprocating tachycardia. CS = coronary sinus; HBE = His bundle electrographic lead; HRA = high right atrium; LA = left atrium; LRA = low septal right atrium.

atrium was activated before the low septal right atrium (in the His bundle electrographic lead) and the high right atrium suggested that the accessory pathway was left-sided.[5,6] However, during right ventricular pacing at an identical cycle length of 600 msec (Fig. 3, B and C), the sequence of retrograde atrial activation revealed that the low septal right atrium adjacent to the normal pathway was activated 20 and 70 msec before the left atrium and the high right atrium, respectively (S_1-LRA_1 = 110 msec; S_1-LA_1 = 130 msec; S_1-HRA_1 = 180 msec). As the premature ventricular coupling interval (V_1-V_2) gradually shortened, there was gradual lengthening of V-A conduction time with a constant temporal relation among the three atrial electrograms (LRA, LA and HRA) (Fig. 3, B and C, and 4) suggestive of retrograde conduction over the normal pathway.[1,2,5,6,10,11] Of note was the observation that the retrograde atrial activation interval (LA_1-LA_2) during programmed ventricular stimulation was constantly beyond the antegrade effective refractory period of the accessory pathway and a paroxysm of reciprocating tachycardia could not be elicited (for example, the LA_1-LA_2 interval of 360 msec at V_1-V_2 intervals of both 320 and 230 msec with respect to the antegrade effective refractory period of the accessory pathway: 300 msec in Figure 3, A to C).

Although the discrepancy in electrophysiologic properties of the two A-V pathways in antegrade and retrograde directions may have limited the use of data from programmed atrial stimulation to explain events seen during programmed ventricular stimulation, we assumed that in this situation concealed retrograde penetration of the accessory pathway in response to premature ventricular stimulation prevented the transmission of an impulse across the accessory pathway in an antegrade direction and thus a circuit of reciprocating tachycardia could not be established.

Group IV: Predominant or exclusive retrograde atrial activation from the accessory pathway (15 patients): Six of these patients had a V-A conduction pattern suggestive of a shift from retrograde atrial fusion to exclusive retrograde atrial activation from the accessory pathway as the premature ventricular coupling interval (V_1-V_2) shortened because the retrograde effective refractory period of the normal pathway was longer than that of the accessory pathway.[1,2] In the remaining nine patients, retrograde atrial activation was exclusively from the accessory pathway throughout the premature coupling intervals (V_1-V_2). Episodes of reciprocating tachycardia could be elicited by programmed ventricular stimulation in only seven of these patients, and it appeared that the induction of reciprocating tachycardia by a premature ventricular beat depended upon the depth of retrograde penetration of the normal pathway.

In four of these latter seven patients, the development of repetitive ventricular responses (V_2V_3 or $V_2V_3V_4$)[12–15] at short coupling intervals (V_1-V_2) resulted, in each instance, in the onset of reciprocating tachycardia (Fig. 5 to 7). At a ventricular driving cycle length of 600 msec, the high right atrium was activated 20 msec before the left atrium (S_1-HRA_1 = 140 msec; S_1-LA_1 = 160 msec; the low septal right atrial electrogram could not be identified with certainty in the His bundle electrographic lead) (Fig. 5, A and B). However, as the premature ventricular coupling interval (V_1-V_2) was decreased to 400 msec, retrograde left atrial activation time remained relatively unchanged (S_2-LA_2 = 160 msec), whereas retrograde high right atrial activation time suddenly lengthened (S_2-HRA_2 = 200 msec). The low septal right atrial electrogram near the normal pathway (in the His bundle electrographic lead) became discernible at this premature coupling interval (V_1-V_2) of 400 msec (S_2-LRA_2 = 180 msec) (Fig. 5A). Further shortening of the premature coupling interval (V_1-V_2) until V-A conduction failed (V_1-V_2 = 200 msec) did not change the sequence of retrograde atrial activation; the left atrium was activated 20 msec and 40 msec before the low septal right atrium and the high right atrium, respectively (Fig. 5B and 6). Therefore, at premature ventricular coupling intervals (V_1-V_2) longer than 400 msec, the atria were being activated from both pathways (retrograde atrial fusion)[2]—the left atrium from the accessory pathway and the high right atrium from the normal pathway. The low septal right atrium was probably activated from the normal pathway, but its electrogram was obscured by the ventricular electrogram in the His bundle electrographic lead.

At premature ventricular coupling intervals (V_1-V_2) of 400 msec or less, the atria were activated exclusively from the accessory pathway.[1,2,5,6,8,9] The minimal increment of V-A conduction time without change in the sequence of atrial activation that occurred between the premature coupling intervals (V_1-V_2) of 270 and 210 msec was due to ventricular latency or intraventricular conduction delay, or both (Fig. 6).[1,2] A zone of reciprocating tachycardia could be defined at premature coupling intervals (V_1-V_2) between 300 and 210 msec, and in each instance, the initiation of reciprocating tachycardia was related to the development of repetitive ventricular responses (V_2V_3 or $V_2V_3V_4$)[12–15] elicited with a single premature stimulus (S_2) at short coupling intervals (V_1-V_2) (Fig. 7, A and B). Under these circumstances, repetitive ventricular responses possibly resulted in progressively less extent of retrograde normal pathway penetration (or retrograde block in the normal pathway); the impulse entered the accessory pathway in a retrograde direction to the atria and then proceeded across the normal pathway in an antegrade direction, establishing a reciprocating tachycardia circuit. Unfortunately, the site of retrograde block in the normal pathway could not be determined utilizing the current method of programmed ventricular stimulation.[1,9,16,17]

In the remaining three patients, a single ventricular response (V_2) could easily elicit an episode of reciprocating tachycardia. Shortening of the basic driving cycle length did not change the V-A conduction pattern and seemed to widen the zone of reciprocating tachycardia. Further shortening of the driving cycle length could by itself initiate and perpetuate reciprocating tachycardia in two of these three patients (Fig. 8 and 9). At ventricular driving cycle lengths of 600 and 510 msec, the longest premature ventricular coupling intervals (V_1-V_2) that elicited reciprocating tachycardia were 450 and 490 msec, respectively (Fig. 8, A and B and 9, A and B). The initiation of reciprocating tachycardia by a single ventricular response (V_2) was possible until V-A conduction failed (270 msec at the two driving cycle lengths of 600 and 510 msec). Therefore, the zone of reciprocating tachycardia was wider with the shorter driving cycle length. A further decrease in the driving cycle length to 450 msec could by itself precipitate and perpetuate reciprocating tachycardia without delivery of a premature stimulus (S_2) (Fig. 8C). This pattern was probably due to early retrograde block in the normal pathway and to a progressive decrease in the depth of retrograde penetration of the normal pathway after a decrease in the ventricular driving cycle length.[16–18]

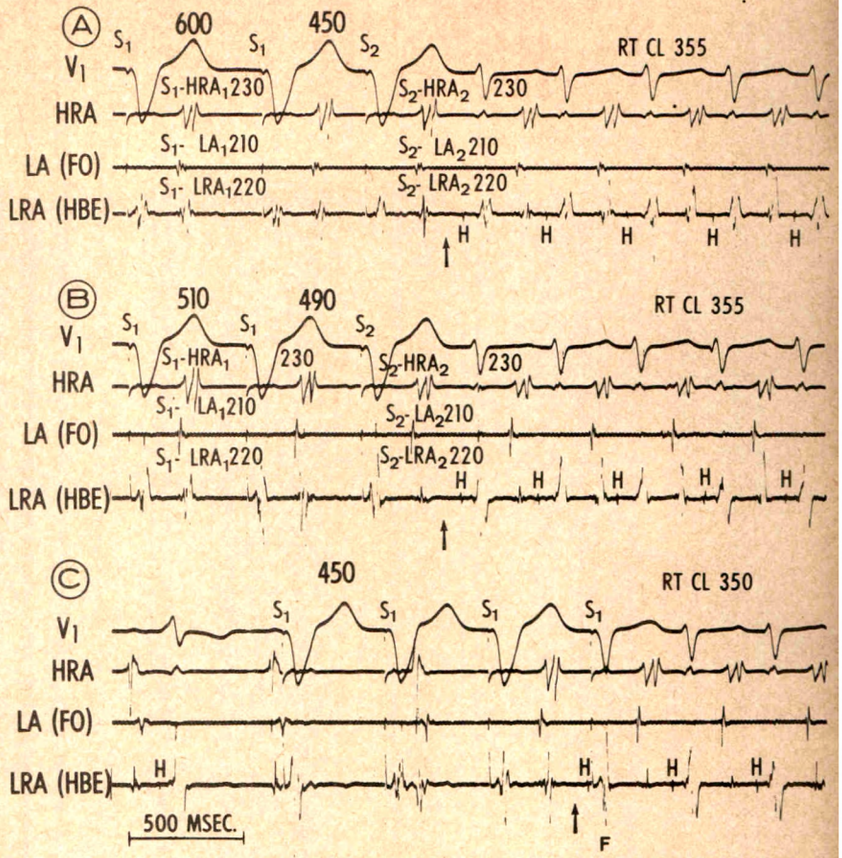


FIGURE 8. A and **B,** during right ventricular pacing (S_1-S_1), the longest premature coupling intervals (S_1-S_2) that can initiate reciprocating tachycardia (RT) **(arrow)** are 450 **(A)** and 490 **(B)** msec at respective driving cycle lengths (CL) of 600 **(A)** and 510 **(B)** msec. The sequence of retrograde atrial activation during pacing and during reciprocating tachycardia suggests that the accessory pathway (AP) is left-sided. **C,** when the right ventricular pacing cycle length is further shortened to 450 msec, a reciprocating tachycardia can be elicited without delivery of premature stimulation (S_2). The sequence of atrial activation corresponding to the first three QRS complexes is that of sinus nodal activity. The third S_1 (the fourth QRS complex) not only captures the right ventricle but also induces a pattern of retrograde atrial activation from the accessory pathway and initiates reciprocating tachycardia **(arrow)**. The fifth QRS complex corresponding to the fourth S_1 is a fusion beat (F). FO = foramen ovale; HBE = His bundle electrographic lead; HRA = high right atrium; LA = left atrium; LRA = low septal right atrium.

Discussion

The introduction of programmed electrical stimulation of the heart combined with the use of intracardiac recordings has advanced understanding of the electrophysiologic mechanisms of paroxysmal tachyarrhythmias in patients with the WPW syndrome.[19–21] Durrer et al.[19] validated that a premature atrial or ventricular beat could initiate reciprocating tachycardia as a result of differences in the electrophysiologic properties of the normal and accessory A-V pathways. In most instances a reciprocating tachycardia involving both A-V pathways utilizes the normal pathway for antegrade conduction and the accessory pathway for retrograde conduction.[4,21] Tachycardia with a conduction circuit of the reverse direction is rare.[1,8,22,23] Therefore, the initiation of a reciprocating tachycardia during programmed atrial stimulation is usually related to antegrade block of an atrial extrasystole in the accessory pathway; conversely, during programmed ventricular stimulation, the initiation of reciprocating tachycardia is frequently associated with retrograde block of a ventricular extrasystole in the normal pathway.

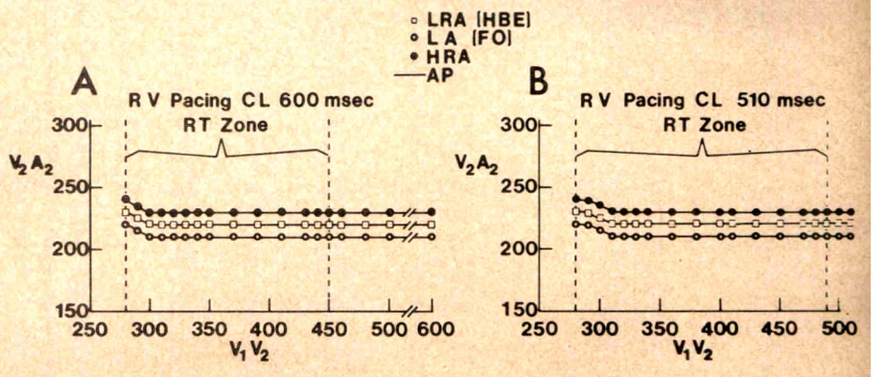


FIGURE 9. Same patient. Retrograde conduction time of premature ventricular beats (V_2-A_2) as a function of premature coupling intervals (V_1-V_2). The ventriculoatrial (V-A) conduction patterns at both right ventricular (RV) cycle lengths (CL) of 600 **(A)** and 510 **(B)** msec indicate exclusive retrograde atrial activation from the accessory pathway (AP). The zone of reciprocating tachycardia (RT) is widened as the pacing cycle length is shortened from 600 to 510 msec and, in every instance, a single ventricular response (V_2) can initiate reciprocating tachycardia. FO = foramen ovale; HBE = His bundle electrographic lead; HRA = high right atrium; LA = left atrium; LRA = low septal right atrium.

Retrograde conduction in the accessory versus normal pathway: The recognition of antegrade block of an atrial extrasystole in the accessory pathway during programmed atrial stimulation is facilitated by the relative ease of discerning the disappearance of the electrocardiographic delta wave and normalization of the corresponding H-V interval. In contrast, the assessment of retrograde conduction during programmed ventricular stimulation is frequently handicapped by uncertainty about the extent of retrograde activation and the exact site of the V-A block in the normal pathway.[1,2,9,16,17] Consequently, the onset of reciprocating tachycardia induced by programmed ventricular stimulation is less predictable than in its atrial counterpart.

When the right ventricular apical endocardium is used as a site for programmed electrical stimulation, the study of retrograde conduction over the accessory pathway, the normal pathway, or both, is complicated by the involvement of many anatomic structures in V-A conduction. The functional electrophysiologic properties of these structures certainly influence the patterns of V-A conduction[1,9,24] and subsequently the initiation of reciprocating tachycardia. For this reason, initiation of reciprocating tachycardia is less frequently observed during programmed ventricular stimulation. In V-A conduction over the accessory pathway, these structures include ventricular myocardium (between the stimulation site and the ventricular end of the accessory pathway), the accessory pathway and the atrium; in V-A conduction over the normal pathway, they include ventricular myocardium, Purkinje network, bundle branches, His bundle, the A-V node and atrium. Nevertheless, the demonstration of various patterns of V-A conduction derived from analysis of retrograde conduction time to each atrial recording site near the normal and the accessory pathways provides some information pertaining to the extent of retrograde conduction over each respective pathway.[2]

Factors initiating reciprocal tachycardia in WPW syndrome: Although our four groups of patients with different V-A conduction patterns in the Wolff-Parkinson-White syndrome is small, some conclusions can be drawn from our results:

1. In patients without V-A conduction (retrograde block in both normal and accessory pathways) (Group I), a reciprocating tachycardia involving both pathways cannot be elicited during programmed atrial or ventricular stimulation because either pathway has to be utilized for retrograde conduction during reciprocating tachycardia.

2. In patients with a V-A conduction pattern of persistent retrograde atrial fusion (Group II), the initiation of reciprocating tachycardia during programmed ventricular stimulation is impossible because collision of impulses from the normal and the accessory pathways constantly occurs at the atrial level (Fig. 2).

3. In patients with a V-A conduction pattern of predominant or exclusive retrograde conduction over the normal pathway (Group III), concealed retrograde penetration of the accessory pathway in response to premature ventricular beats (Fig. 3), and certainly the likelihood of development of early retrograde block in the normal pathway at short premature ventricular coupling intervals (V_1-V_2) (which usually occurs in the A-V node),[16,17] may prevent the initiation of a reciprocating tachycardia. In this situation, three conditions must be fulfilled for initiation and perpetuation of a reciprocating tachycardia utilizing the normal pathway for retrograde conduction and the accessory pathway for antegrade conduction: (a) a normal pathway with a short retrograde effective refractory period allowing constant V-A conduction over the normal pathway; (b) an accessory pathway with a short antegrade effective refractory period; and (c) absence or minimal extent of retrograde penetration of the accessory pathway in response to premature ventricular beats. The initiation of this type of reciprocating tachycardia during programmed ventricular stimulation is uncommon.[1]

4. In patients with a V-A conduction pattern of predominant or exclusive retrograde conduction over the accessory pathway (Group IV), predicting the initiation of reciprocating tachycardia during programmed ventricular stimulation is limited by the uncertainty about the depth of retrograde penetration of the normal pathway[1,2,9,16,17] because the His bundle electrogram is usually obscured by the ventricular electrogram. Reciprocating tachycardia may not be elicited in certain patients because of the great extent of concealed retrograde penetration of the normal pathway which prevents the impulse from being transmitted in antegrade fashion over it. Therefore, the development of repetitive ventricular responses (V_2V_3 or $V_2V_3V_4$)[12–15] at short premature ventricular coupling intervals (V_1-V_2) may be required to initiate reciprocating tachycardia (Fig. 7, A and B).

The genesis of repetitive ventricular responses (V_2V_3 or $V_2V_3V_4$) induced at short premature coupling intervals (V_1-V_2) has been attributed to reentry occurring in the bundle branch system or in the local myocardium at the stimulation site.[12–15] In any event, the effect of repetitive ventricular responses (V_2V_3 or $V_2V_3V_4$) at short coupling intervals (V_1-V_2) is similar to that of delivering two or three consecutive premature ventricular stimuli, which probably results in progressively less extent of retrograde penetration of the normal pathway (or retrograde block in the normal pathway). This consequently favors induction of a reciprocating tachycardia in patients with the WPW syndrome.[4,23] If retrograde penetration of the normal pathway is less deep during the basic driving cycle length, a single premature ventricular beat (V_2) can easily induce reciprocating tachycardia. Additionally, shortening of the driving cycle length may either widen the zone of reciprocating tachycardia or in itself initiate and perpetuate reciprocating tachycardia (Fig. 8 and 9), or do both, by virtue of producing progressively less deep retrograde penetration of the normal pathway (or earlier retrograde block in the normal pathway).[16–18]

Implications: Our study further demonstrates the importance of differences in the electrophysiolgic properties of the two A-V conduction pathways in the

genesis of reciprocating tachycardia in the WPW syndrome. The initiation of reciprocating tachycardia during programmed ventricular stimulation is related to various patterns of V-A conduction. Except in patients without V-A conduction, the initiation of reciprocating tachycardia generally depends on the depth of retrograde penetration of the normal pathway induced by premature ventricular beats; the less this depth, the more easily can reciprocating tachycardia be elicited.

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Chronic Recurrent Right and Left Ventricular Tachycardia: Comparison of Clinical, Hemodynamic and Angiographic Findings

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Twenty-seven patients with chronic recurrent ventricular tachycardia were judged to have either left or right ventricular tachycardia on the basis of electrocardiographic QRS configuration during the tachycardia. Clinical, hemodynamic and angiographic evaluation was performed. The 15 patients who had left ventricular tachycardia were older (mean age 43 years) and predominantly male (male/female ratio 10:5), and all (100 percent) had diagnosable organic heart disease. The 12 patients who had right ventricular tachycardia were younger (mean age 32 years) and mostly female (male/female ratio, 4:8), and only three (25 percent) had diagnosable organic heart disease. Patients with left ventricular tachycardia had lower cardiac output and a much greater prevalence of abnormal left ventricular and coronary angiograms than patients with right ventricular tachycardia. Patients with left ventricular tachycardia were followed up for an average of 38 months (one patient lost to follow-up); three deaths occurred. Patients with right ventricular tachycardia were followed up for 35 months (two patients lost to follow-up); none died. Grouping of patients with chronic recurrent ventricular tachycardia into those with left or right ventricular tachycardia appears to be useful. The latter condition appears to be less serious.

Cardiac stimulatory studies suggest that the site of origin of ventricular ectopic beats can be identified by QRS configuration.[1–4] Right ventricular ectopic beats are characterized by QRS complexes with a pattern of left bundle branch block. In contrast, ectopic beats originating from the left ventricle are characterized by a pattern of right bundle branch block.

Although it has been suggested that left ventricular premature beats imply the presence of organic heart disease, little is known regarding the clinical significance of the site of ventricular tachycardia.[5] In this study, we describe and compare patients with chronic recurrent right or left ventricular tachycardia. Our results suggest that the two conditions have a different clinical significance.

Materials and Methods

Patient classification: Twenty-seven patients with chronic recurrent unifocal ventricular tachycardia were evaluated clinically and underwent diagnostic cardiac catheterization between February 1971 and August 1975 in the Chicago West Side Medical Center. Eleven of the 27 patients were referred specifically for evaluation of arrhythmias by physicians outside of the medical center. No patient was included in this study who had had a myocardial infarction within 1 year of diagnosis of ventricular tachycardia, or who had been subjected to a drug or pacing catheter that might have induced ventricular tachycardia.

Ventricular tachycardia was diagnosed utilizing standard electrocardiographic criteria, that is, a prolonged QRS complex (27 patients), atrioventricular

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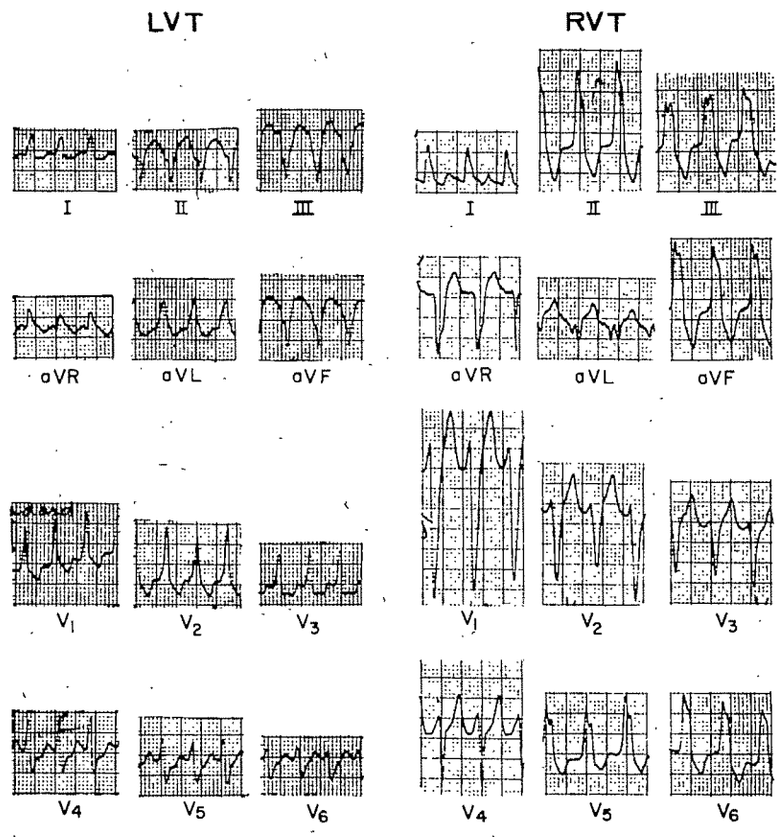


FIGURE 1. Twelve-lead electrocardiograms demonstrating typical examples of left ventricular tachycardia (LVT) (**left**) and right ventricular tachycardia (RVT) (**right**). Note the right bundle branch block pattern at left and the left bundle branch block pattern at right.

(A-V) dissociation (27 patients), fusion beats (13 patients) and normal QRS capture beats (9 patients). Ventricular tachycardia was additionally verified with His bundle recordings in 11 patients, including all in whom there was any question regarding diagnosis of ventricular tachycardia. Both the duration and frequency of ventricular tachycardia were determined utilizing symptoms and electrocardiograms. The term "chronic recurrent" defined a minimum of two documented episodes of ventricular tachycardia at least 1 month apart. In the majority of patients this minimal frequency was greatly exceeded. Patients were classified as having either "sustained" or "nonsustained" ventricular tachycardia. "Sustained" referred to protracted paroxysms of tachycardia usually terminated with pharmacologic or electrical intervention. In these patients, episodes of ventricular tachycardia were separated by periods of sinus rhythm for as long as 6 months and intervening electrocardiograms usually did not show premature ventricular contractions. "Nonsustained" ventricular tachycardia was characterized by frequent short self-terminating episodes with many premature ventricular beats (usually identical in configuration to QRS complexes during ventricular tachycardia) in most or all electrocardiograms.

The patients were classified into two groups, utilizing the following electrocardiographic criteria: Right ventricular tachycardia was diagnosed on the basis of demonstration of ventricular tachycardia with a left bundle branch block pattern. Left ventricular tachycardia was diagnosed when QRS complexes had a right bundle branch block pattern (Fig. 1).

Hemodynamic evaluation: Intracardiac pressures at rest were recorded in all the heart chambers and major vessels. Cardiac output was determined using the Fick principle, with blood samples obtained from the pulmonary artery and aorta analyzed with the method of Van Slyke, and expired air analyzed for oxygen and carbon dioxide with the Scholander method.[6] Left ventricular angiograms were performed in the 30° right anterior oblique projection. Ejection fraction and mean velocity of circumferential fiber shortening were calculated as previously described.[7-9] Abnormalities in segmental left ventricular contraction were localized and assessed qualitatively. Selective coronary arteriograms were obtained in 23 patients, using either a femoral or a brachial arterial approach.

Clinical diagnosis: Criteria for the diagnosis of coronary artery disease included the presence of typical exertional angina pectoris or previously documented myocardial infarction, or both. In most patients, the diagnosis of coronary artery disease was further substantiated with coronary arteriographic demonstration of significant (greater than 75 percent) obstruction of luminal diameter in one or more coronary arteries. Primary myocardial disease was diagnosed when there was clinical evidence of congestive heart failure or hemodynamic evidence of left or right ventricular dysfunction, or both, in the absence of demonstrable cause. Idiopathic ventricular tachycardia was diagnosed when there were no clinical findings of heart disease other than ventricular tachycardia and clinical, hemodynamic and angiographic (both ventricular and coronary) studies were normal.

Student's unpaired t test and the Fischer Exact test were used to assess the significance of differences between patients with right and left ventricular tachycardia.

Results

Left Ventricular Tachycardia

Fifteen patients could be classified as having chronic recurrent left ventricular tachycardia; the condition was

considered sustained in 11 patients and nonsustained in 4. The patients had had chronic recurrent left ventricular tachycardia for 1 to 139 (38.3 ± 8.9 [mean ± standard error of the mean]) months, with observed rates ranging from 88 to 250 (mean 169 ± 10) beats/min. Individual variation in the rate of ventricular tachycardia of 58 (range 14 to 100) beats/min occurred in nine patients.

Clinical and electrocardiographic findings: The mean age at onset of left ventricular tachycardia was 42.9 ± 5.5 (range 8 to 66) years. Ten patients were male and five female. All patients were symptomatic, 12 with palpitation, 5 with syncope, 6 with chest pain (2 patients had typical angina pectoris) and 7 with dyspnea. Four patients had a history of prior myocardial infarction and another had a history of angina pectoris. Two had known congenital heart disease, one with Ebstein's anomaly and one with surgically corrected tetralogy of Fallot. Another patient had a long history of hypertension. Five had normal cardiovascular physical findings; the remaining patients had abnormal heart sounds or murmurs, or both. With the exception of ventricular arrhythmia, the resting electrocardiogram was normal in four patients; in the remaining patients it was abnormal. Abnormal findings included residual Q waves of old myocardial infarction (four patients), right or left bundle branch block (five patients), left anterior superior hemiblock, left ventricular hypertrophy (two patients), nonspecific ST-T wave changes (two patients) and first degree A-V block (four patients).

Cardiac catheterization (Table IA): Resting left ventricular end-diastolic pressure was elevated in 7 of 15 patients, and mean pulmonary capillary wedge pressure was abnormal in 1 of 12 patients. For the group, mean right atrial, right ventricular end-diastolic and pulmonary arterial pressures were normal; however, three patients had elevated right atrial pressure, five had elevated right ventricular end-diastolic pressure and four had elevated pulmonary arterial pressure.

Cardiac index was less than 2.4 liters/min per m^2 in 4 of 12 patients. Ejection fraction was less than 0.53 and mean velocity of circumferential muscle fiber shortening was less than 1.1 circumferences/sec in 11 of 14 patients.

TABLE I

Cardiac Catheterization Data

Case no.	Pressures (mm Hg) RA	RVEDP	PA	PCW	LVEDP	CI	EF	$\overline{V}cf$	Segmental LV Contraction	Coronary Arteriogram
					A. Left Ventricular Tachycardia					
1	8	9	39	30	29	3.2	25	0.71	Akinesia, anteroapical	LCx 30%, LAD 100%
2	3	4	16	7	14	2.3	37	0.73	Dyskinesia, anteroapical	Diagonal 100%, LAD 95%, LCx 35%
3	3	7	16	4	11	2.4	58	0.71	Hypokinesia, inferior	RCA 75%, LAD 30%
4	3	4	18	6	12	2.1	32	0.35	Akinesia, posterobasal; hypokinesia, apical	LCx 90%, RCA 90%
5	5	6	19	9	14	2.2	29	0.18	Akinesia, posterobasal; dyskinesia, anterior	Not performed for technical reasons
6	3	8	20	...	21	2.6	38	0.71	Akinesia, apical	LAD 75%, LCx 75%, RCA 50%
7	3	3	13	5	11	2.6	67	2.0	Normal	Normal
8	7	6	17	10	10	...	...	0.88	Normal	Not performed
9	5	10	14	7	8	2.9	60	0.98	Normal	Not performed
10	5	9	30	7	16	2.5	25	0.32	Hypokinesia, diffuse	Normal
11	...	2	12	6	2	1.9	49	1.1	Normal	Normal
12	12	10	23	...	18	...	51	1.1	Normal	Normal
13	...	...	...	...	16	...	35	...	Hypokinesia, diffuse	Normal
14	...	...	18	8	6	2.6	51	0.93	Normal	Normal
15	1	3	9	7	12	3.0	40	0.6	Hypokinesia, posterobasal	Normal
					B. Right Ventricular Tachycardia					
16	6	6	15	10	8	6.8	69	1.5	Normal	Normal
17	1	3	8	9	7	3.8	64	1.5	Normal	Normal
18	3	7	14	9	9	3.6	61	1.4	Normal	Normal
19	1	1	9	8	11	3.4	62	1.9	Normal	Normal
20	3	2	16	...	...	2.8	...	...	...	...
21	2	4	11	8	7	3.3	59	1.2	Normal	Normal
22	4	7	12	7	12	2.4	77	1.8	Normal	Normal
23	4	7	17	10	12	4.0	54	1.2	Normal	Normal
24	5	7	12	6	5	2.4	77	1.8	Normal	Normal
25	11	10	19	14	6	4.5	76	2.5	Normal	Normal
26	5	6	12	9	8	3.4	50	0.7	Normal	Normal
27	7	9	27	25	31	1.5	21	0.3	Hypokinesia, diffuse	Normal

* Percentages indicate percent luminal narrowing.

CI = cardiac index (liters/min per m^2); EF = ejection fraction (%); LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVEDP = left ventricular end-diastolic pressure; PA = mean pulmonary arterial pressure; PCW = mean pulmonary capillary wedge or left atrial pressure; RA = mean right atrial pressure; RCA = right coronary artery; RVEDP = right ventricular end-diastolic pressure; $\overline{V}cf$ = mean velocity of circumferential muscle fiber shortening (circumferences/sec).

Left ventricular contraction was abnormal in nine patients, seven with segmental defects and two with diffuse hypokinesia. One patient (Case 13) had prolapse of the mitral valve. Coronary arteriography revealed high grade obstructive lesions (more than 75 percent of luminal diameter) in one or more coronary arteries in 4 of 14 patients.

Diagnosis and follow-up: On the basis of history, physical examination, electrocardiogram and cardiac catheterization data, all patients with left ventricular tachycardia had diagnosable organic heart disease. Of these, six patients had coronary artery disease, six had primary myocardial disease (diagnosed in four on the basis of presence of left ventricular dysfunction during cardiac catheterization), one had hypertensive cardiovascular disease and two others had congenital heart disease (Ebstein's anomaly and tetralogy of Fallot).

Patients were followed up an average of 38.3 ± 8.9 (range 1 to 139) months after electrocardiographic diagnosis of left ventricular tachycardia. Two patients died suddenly, and two deaths were not sudden; 11 patients are living, including one lost to follow-up.

Right Ventricular Tachycardia

There were 12 patients with chronic recurrent right ventricular tachycardia; the condition was judged sustained in 4 patients and nonsustained in 8. It had been present from 3 to 94 (mean 34.8 ± 9.5) months, with observed rates ranging from 86 to 260 (mean 158 ± 12) beats/min. Individual variation in the rate of ventricular tachycardia of 41 (range 10 to 100) beats/min occurred in seven patients.

Clinical and electrocardiographic findings: The mean age at onset of right ventricular tachycardia was 31.7 ± 4.0 (range 9 to 52) years. Eight of the 12 patients were female and 4 were male. All but 1 was symptomatic; 10 with palpitation, 5 with syncope, 2 with atypical chest pain and 2 with dyspnea. Ten patients had a normal cardiovascular examination, one patient had cardiomegaly and gallop rhythm and another had a pansystolic murmur. With the exception of ventricular arrhythmia, the resting electrocardiogram was normal in 10 patients; it was abnormal in 2. The abnormal findings included nonspecific ST-T wave changes in one patient and left anterior superior hemiblock in another.

Cardiac catheterization (Table IB): Nine patients had normal hemodynamics, left ventricular contraction and coronary arteriograms. The three remaining patients had normal coronary arteriograms but abnormal hemodynamics. One patient (Case 27) had abnormal right and left heart pressures, depressed cardiac output and contractile indexes and a diffusely hypokinetic left ventricle. Another (Case 25) had abnormal right atrial, right ventricular end-diastolic and pulmonary capillary wedge pressures. The remaining patient (Case 26) had only moderately depressed left ventricular contractile indexes.

Diagnosis and follow-up: On the basis of history, physical examination, electrocardiogram and cardiac catheterization, 9 of the 12 patients had no evidence of organic heart disease; the remaining 3 were judged to have primary myocardial disease (1 with clinically apparent cardiomyopathy and 2 with minor abnormalities during cardiac catheterization). Patients were followed up an average of 34.8 ± 9.5 (range 3 to 94) months after the electrocardiographic diagnosis of right ventricular tachycardia. Ten are living and two have been lost to follow-up.

Comparison of Patients With Left or Right Ventricular Tachycardia

Patients with left ventricular tachycardia were older (mean age left versus right ventricular tachycardia 42.9 ± 5.5 versus 31.7 ± 4.0 years) and had a male predominance (male/female ratio 10:5 versus 4:8). All patients with left ventricular tachycardia had diagnosable organic heart disease and four (26 percent) died during the mean follow-up period of 38 months. In contrast, patients with right ventricular tachycardia had a significantly lower incidence rate (25 percent) of heart disease ($P < 0.001$) and none died during the 35 month follow-up period.

Discussion

Means of localizing site of ventricular tachycardia: Right ventricular stimulation produces a QRS complex with a pattern of left bundle branch block, and left ventricular stimulation a pattern of right bundle branch block. Spontaneous premature beats presumably behave similarly, allowing the site of origin of spontaneous ectopic beats to be identified.[1–4] It has been suggested that ectopic beats arising from the right ventricle are benign compared with those originating from the left ventricle.[2,5] Despite the ability to predict the site of origin of ventricular ectopic beats, little is known regarding the clinical significance of the site of origin of ventricular tachycardia.

In patients with a ventricular aneurysm and ventricular tachycardia, surgical excision of the aneurysm to control recurrent ventricular tachycardia resistant to medical management has had a moderate degree of success.[10–23] Review of such cases partially supports the proposed use of electrocardiographic localization of ventricular tachycardia. In patients with electrocardiographic left ventricular tachycardia, excision of the left ventricular aneurysm resulted in amelioration of the tachycardia.[19–23] Curiously, the condition of four patients with electrocardiographic right ventricular tachycardia similarly improved after left ventricular aneurysmectomy.[10,22–24] Tomisawa et al.[25] described one patient whose right ventricular tachycarida, diagnosed electrocardiographically, was abolished by right ventricular aneurysmectomy. Excision of a left ventricular tumor in two children with electrocardiographic left ventricular tachycardia abolished this arrhythmia.[26] With the exception of findings in the four patients with right ventricular tachycardia and left ventricular aneurysmectomy, these data indicate the validity of the proposed electrocardiographic localization of ventricular tachycardia.

TABLE II

Comparison of Current Series and Reported Cases[10,19-46]

	Left Ventricular Tachycardia		Right Ventricular Tachycardia	
	Current Series	Previously Reported	Current Series	Previously Reported
Patients (no.)	15	48	12	25
Age (yr)	43	53	32	36
Sex (male:female)	10:5 (75%)	41:7 (85%)*	4:8 (66%)	12:13 (52%)*
Presence of organic heart disease	15 (100%)*	42 (88%)*	3 (25%)*	12 (48%)*
Absence of heart disease	0 (0%)*	6 (12%)*	9 (75%)*	13 (52%)
Deaths	4 (26%)	5 (10%)	0 (0%)	3 (12%)

* Significant differences between patient groups with left or right ventricular tachycardia in the current series and in reported cases.

Epicardial mapping provides the most definitive means of documenting the electrocardiographic predicted site of origin of ventricular tachycardia. Three patients with electrocardiographic left ventricular tachycardia have had such mapping.[27-29] The tachycardia appeared to arise from the posterior aspect of the left ventricle at the margin of a large apical aneurysm in one, from the anterior surface of the left ventricle adjacent to the distal one third of the left anterior descending coronary artery in one, and from the margin of the left ventricle in one. Two other patients with electrocardiographic right ventricular tachycardia also underwent mapping.[28,29] The tachycardia appeared to arise on the anterior surface of the right ventricle adjacent to the anterior intraventricular groove in one, and from the right ventricular margin in the other. Epicardial mapping, performed in animals with electrocardiographic left ventricular tachycardia induced by ouabain and acetylstrophanthidin, demonstrated left ventricular tachycardia arising from the left ventricle.[30]

Review of reported cases*: A review of cases of recurrent ventricular tachycardia not associated with acute myocardial infarction yielded 73 instances with sufficient reported electrocardiographic data to allow classification as left or right ventricular tachycardia (Table II).[10,19-46] We identified 48 patients with left ventricular[20,23,25,28,29,34,37,39-46] and 25 with right ventricular[10,19-24,26-29,31-42] tachycardia. Compared with the patients with right ventricular tachycardia, the 48 patients with left ventricular tachycardia were significantly older (53.3 ± 2.6 years) and predominantly male (85 percent); the majority (88 percent) had organic heart disease, and all five who died (10 percent) had organic heart disease. In contrast, the 25 patients with right ventricular tachycardia were significantly younger (36 ± 3.5 years); 13 (52 percent) were female and only 12 (48 percent) had organic heart disease; three patients (12 percent) died, two of whom had no organic heart disease.

Comparison with our series: Review of the reported cases generally supports our results. As in our series, patients in the reported series with left ventricular tachycardia were older, had organic heart disease and had a male predominance. In 6 (12 percent) of the reported cases, the patients with left ventricular tachycardia had a "normal" heart, whereas all our patients with left ventricular tachycardia had organic heart disease. There were twice as many patients with organic heart disease in the reported series with right ventricular tachycardia as in our series (48 versus 25 percent). In the reported cases, right ventricular tachycardia could be associated with chronic arteriosclerotic heart disease, an association not seen in our series. Some of the differences between our series and previously reported cases may be explained by case selection. Most reports were based not on consecutive patient studies, but rather on small series of cases reported because of specific diagnostic findings or therapeutic responses. The greater incidence of organic heart disease in our patients with left ventricular tachycardia probably reflects in part the fact that all our patients had diagnostic cardiac catheterization.

Clinical implications: Our study suggests that patients with chronic recurrent left ventricular tachycardia differ from those with right ventricular tachycardia in that they are older, predominantly male and are more likely to have organic heart disease and significant mortality. They frequently have reduced cardiac output, abnormal left ventricular contraction and demonstrable coronary artery disease. In contrast, patients with chronic recurrent right ventricular tachycardia are younger, predominantly female, have a low prevalence rate of organic heart disease and a good prognosis. They frequently have normal hemodynamics and normal coronary arteriograms.

The clinical course of patients with chronic recurrent left or right ventricular tachycardia has been variable, with many patients having frequent recurrences, whether or not they were receiving antiarrhythmic therapy. In some patients the tachycardia has been abolished with therapy; in others it has apparently ceased spontaneously. Mortality appeared to be primarily influenced by the presence of underlying organic heart disease rather than arrhythmia. The need and efficacy of antiarrhythmic therapy for chronic recurrent tachycardia of both left and right ventricular origin require further investigation.

* A tabulation of reported cases of chronic recurrent left and right ventricular tachycardia can be obtained from the authors on request.

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Direct and Reflex Cardiostimulating Effects of Hydralazine

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Increased cardiac output and heart rate after administration of hydralazine have been attributed to reflex activation of the cardiac sympathetic nerves secondary to the decrease in arterial pressure. However, some studies suggest that hydralazine has an additional direct cardiostimulatory effect. The present study was designed to investigate this possibility. Mean arterial pressure, percent change in myocardial contractile force using a Walton-Brodie strain gauge and heart rate were measured in eight open chest dogs anesthetized with sodium pentobarbital. After intravenous administration of hydralazine, 20 mg, myocardial contractile force increased on average by 27 percent and heart rate by 7 percent; mean arterial pressure decreased less than 10 percent. The same reduction of mean arterial pressure with sodium nitroprusside resulted in increases of only 10 percent in myocardial contractile force and 2 percent in heart rate. The differences between the drugs were statistically significant for heart rate ($P < 0.05$) and myocardial contractile force ($P < 0.01$). After reductions in mean arterial pressure exceeding 10 percent, the increases in heart rate and myocardial contractile force with either hydralazine or sodium nitroprusside were insignificantly different. Direct injection of 0.8 mg of hydralazine into a coronary artery in four dogs consistently increased myocardial contractile force in the area perfused whereas administration of sodium nitroprusside even in large doses exerted no local inotropic activity. The local effect of hydralazine was blocked by intravenous administration of propranolol. These results suggest that the increase in myocardial contractile force and heart rate after administration of hydralazine is the result not only of a reflex response to a decrease in blood pressure, as occurred with sodium nitroprusside, but also of direct beta adrenergic stimulation of myocardium.

Hydralazine decreases blood pressure by a direct vasodilator effect on the arterioles,[1–3] the reduction being associated with an increase in cardiac output and heart rate. The cardiac effects are inhibited by beta adrenergic blocking drugs[4–6] and have been attributed solely to a reflex activation of the cardiac sympathetic nerves secondary to the decrease in blood pressure. However, studies by several investigators have suggested that hydralazine may have an additional direct stimulating effect on the myocardium.[7,8] The purpose of this study was to determine whether hydralazine has such an effect in addition to the well known reflex action of vasodilator drugs.

Material and Methods

Sodium nitroprusside, a vasodilator drug, presumably exerts only reflex cardiac stimulatory effects and has no direct inotropic or chronotropic activity. It was used as the control agent to compare the hemodynamic effects of hydralazine. Two experimental designs were employed to study the effects of both systemic administration and local coronary injection of hydralazine on myocardial contractility.

1. *The effects of systemic injection of hydralazine* were studied in eight open chest mongrel dogs weighing 18 to 22 kg anesthetized with intravenously ad-

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ministered sodium pentobarbital. They were ventilated artificially with a Harvard pump. The right femoral artery and vein were surgically exposed and cannulated with no. 6 Kifa catheters. After the arterial catheter was advanced to the ascending aorta the blood pressure was recorded with a Statham P23Db strain gauge transducer. A venous catheter was advanced into the inferior vena cava for the purpose of drug administration. After exposure of the heart, a Walton-Brodie strain gauge was sutured to the left ventricle to monitor myocardial contractility. Heart rate was determined from the electrocardiogram.

Sodium nitroprusside, 50 mg dissolved in 500 ml of 5 percent dextrose in water, was infused through the venous catheter. The rate of infusion was gradually increased from 100 to 300 μg/min until the desired hypotensive effect was obtained. When the hemodynamic effects of the nitroprusside had worn off, 20 mg of hydralazine was given intravenously as a bolus injection. After disappearance of the effects of hydralazine on heart rate and arterial blood pressure, beta adrenergic blockade was induced by administering 6 to 10 mg of propranolol intravenously. The presence of beta adrenergic blockade was validated by injecting 10 μg of isoproterenol intravenously to determine whether the cardiostimulatory effect of the latter drug was blocked. A second dose of 20 mg of hydralazine was then given intravenously, and its effect on heart rate and myocardial contractility was recorded.

2. *The effects of local administration of hydralazine on the myocardium* were studied in four open chest anesthetized mongrel dogs weighing 22 to 26 kg. After exposure of the heart, a side branch of the left anterior descending coronary artery was dissected free and a Teflon® catheter (inner diameter 0.027 inch [0.69 cm], outer diameter 0.039 inch [0.991 cm]) was inserted and positioned at the junction of the branch with the main coronary artery so as to avoid obstructing flow in the latter vessel. Evans blue dye, 1 ml, was injected through the catheter to define visually the area perfused by the left descending coronary artery distal to the side branch. A Walton-Brodie strain gauge was then sutured in this area of the left ventricle. A second control Walton-Brodie gauge was sutured to a remote area of the myocardium not perfused by the catheterized segment (Fig. 1). The small doses used for local perfusion of the myocardium were far smaller than those required for eliciting the reflex cardiovascular effects of hy-

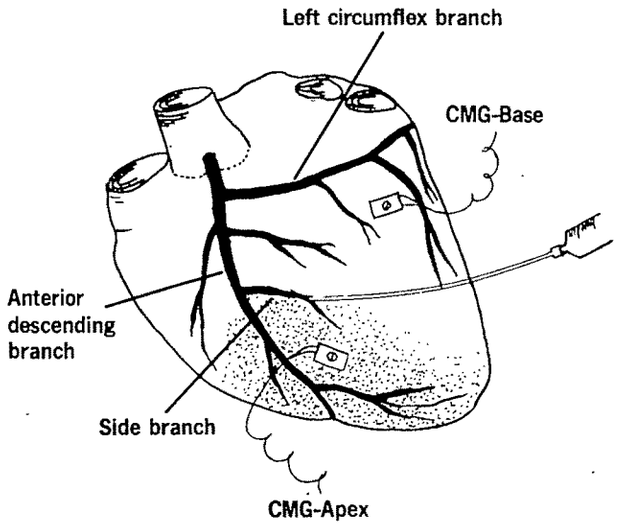


FIGURE 1. Preparation used for studying local effects of drugs on the myocardium. CMG = cardiomyogram (Walton-Brodie gauge).

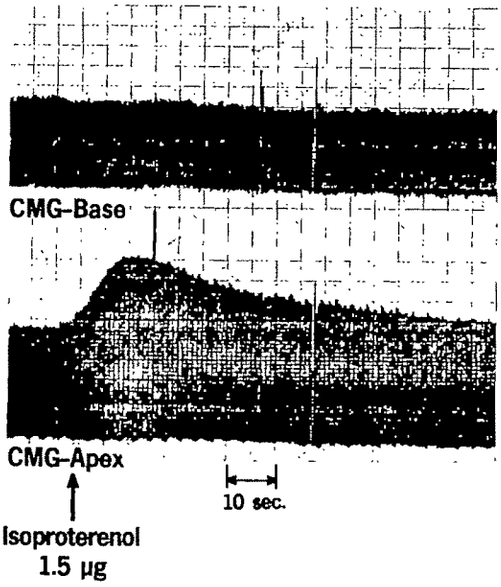


FIGURE 2. Increase of contractile force in the apical region of the left ventricle after injection of 1.5 μg of isoproterenol into the descending branch of the left coronary artery. The cardiomyogram (CMG) at the ventricular base remains unchanged.

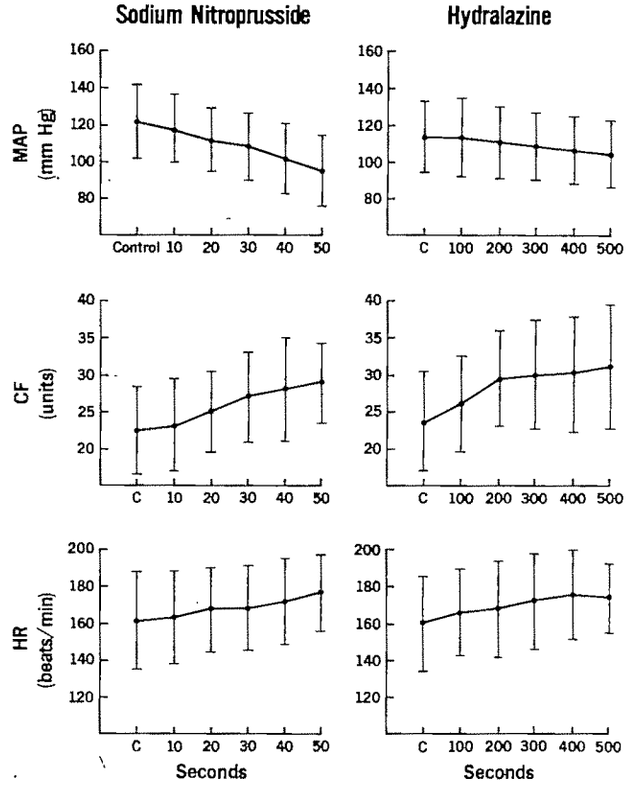


FIGURE 3. Average changes in mean arterial pressure (MAP), contractile force (CF) and heart rate (HR) in eight dogs after systemic administration of sodium nitroprusside and hydralazine. **Vertical bars** represent standard deviations. C = control.

dralazine. The local responsiveness of the myocardium was tested by injecting 1.5 μg of isoproterenol into the coronary artery. This resulted in a sharp increase of contractility in the perfused area of myocardium, whereas the nonperfused area remained unaffected (Fig. 2). The volume of all of the intracoronary injectates was limited to 1 ml or less. To exclude the effect of volume alone on myocardial contractility 1 ml of normal saline solution was injected before any drug was given. This injection did not affect contractility in the perfused myocardial segment.

The initial dose of sodium nitroprusside administered locally into the coronary artery was 20 μg. The dose was doubled if no local effect was observed and was further increased until there was a decrease in blood pressure indicating a systemic effect. This effect was usually observed at a dose of about 120 μg. Increasing doses of hydralazine were similarly given starting at 0.2 mg and the dose was usually increased to a maximum of 0.8 mg. Similar doses of hydralazine were injected after systemic beta adrenergic blockade.

Results

Systemic effects of hydralazine and sodium nitroprusside: Both hydralazine and sodium nitroprusside administered intravenously significantly reduced blood pressure (Fig. 3). During the infusion of sodium nitroprusside, there was no change in heart rate or in myocardial contractility until the mean arterial pressure decreased (Fig. 4). By contrast, after the intravenous injection of 20 mg of hydralazine, there was a progressive increase in myocardial contractility and heart rate before any significant reduction in blood pressure. Figure 3 compares the effects of hydralazine and sodium nitroprusside on blood pressure, myocardial contractility and heart rate in eight dogs. During the first 200 seconds after administration of hydralazine there was a marked increase in heart rate and myocardial contractility despite only a modest decrease in mean arterial pressure. By contrast, with sodium nitroprusside similar increases in heart rate and contractile force were associated with considerably greater decreases in blood pressure (Fig. 3).

The initial increase in myocardial contractility and heart rate that occurred after the administration of hydralazine was associated with minimal or no reduction in blood pressure, but subsequent increases in contractility after hydralazine were related in time and degree to the decrease in blood pressure. Figure 5 compares the percent change in contractile force and heart rate with 0 to 10 percent reduction in blood pressure after administration of hydralazine and sodium nitroprusside. After injection of hydralazine, contractile force increased by 27 percent and heart rate by 7 percent. After a similar decrease in blood pressure (averaging 5.7 mm Hg) with sodium nitroprusside, there was only a 10 percent increase in contractile force associated with a 1.7 percent increase in heart rate. However, with a greater decrease in mean arterial pressure (more than 10 percent of control value), the differences between the two drugs with respect to contractile force and heart rate were no longer significant (Fig. 3). After effective

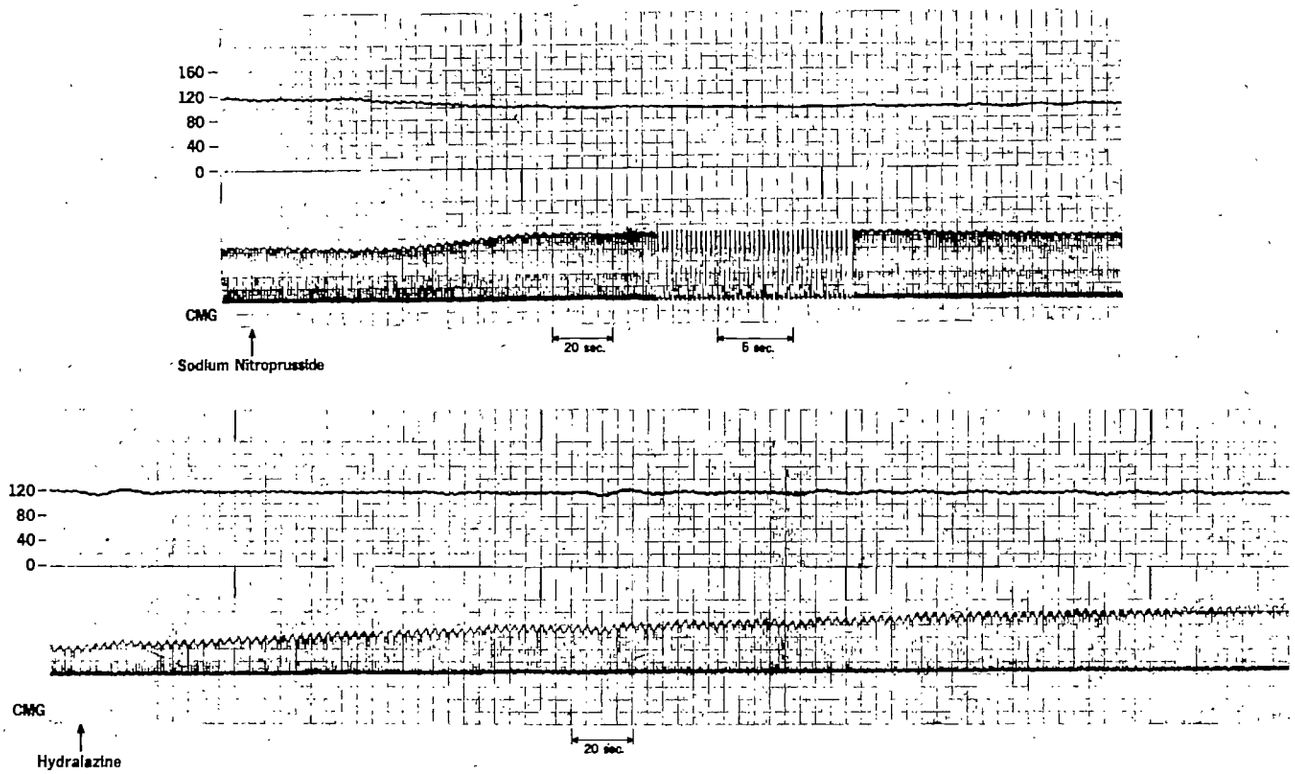


FIGURE 4. Top tracing, effect of intravenous infusion of sodium nitroprusside on the mean arterial pressure (ordinate, mm Hg) and myocardial contractility, measured with the cardiomyogram (CMG). **Bottom tracing,** effect on mean arterial pressure and myocardial contractility after intravenous injection of 20 mg of hydralazine.

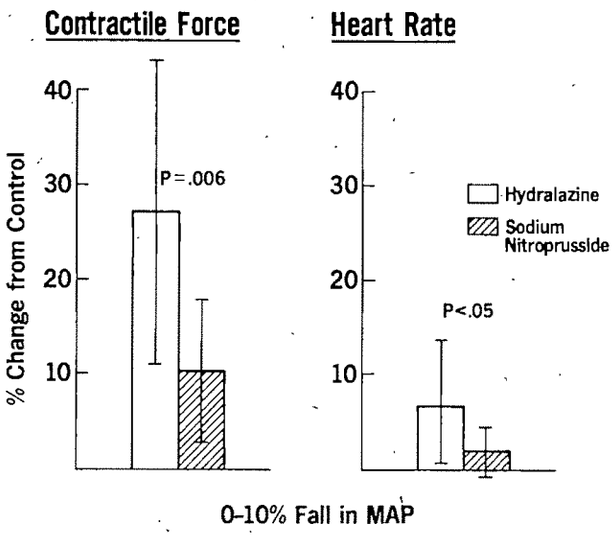


FIGURE 5. Percent change in myocardial contractile force and heart rate from the control values after infusion of sodium nitroprusside and hydralazine, 0.8 mg, are compared for the same quantitative reduction in mean arterial pressure (MAP) expressed as percent change from control. **Vertical bars** indicate standard deviations. P = probability.

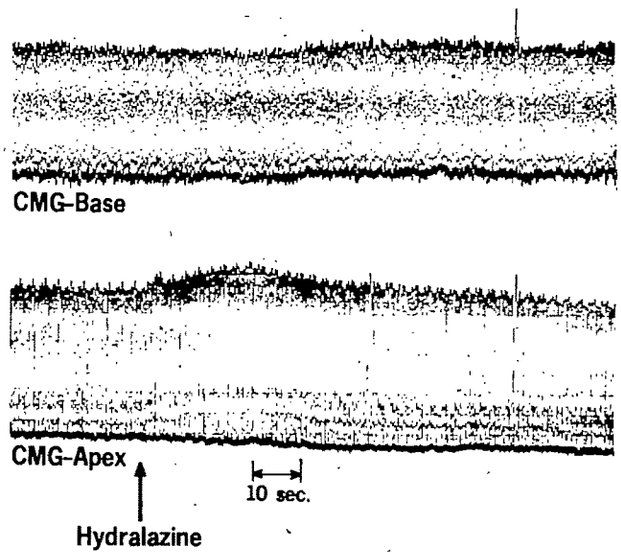


FIGURE 6. Rise in myocardial contractile force in the apical region of the left ventricle after injection of 0.8 mg of hydralazine into the descending branch of the left coronary artery. The cardiomyogram (CMG) at the base remains essentially unchanged.

beta adrenergic blockade with propranolol, both the early and the late effects on heart rate and contractile force were blocked.

Local effect of hydralazine and sodium nitroprusside: Intracoronary injection of 0.8 mg of hydralazine, which represented only 4 percent of the systemic dose, increased the contractility of the perfused myocardium (Fig. 6) whereas the nonperfused segment remained unchanged. Intracoronary arterial injection of sodium nitroprusside in doses of 20 to 100 μg failed to produce any effect on the perfused myocardium. However, 120 μg injected as a bolus dose into the coronary artery resulted in a reduction of arterial pressure and consequent increase in myocardial contractile force and heart rate. After systemic beta adrenergic blockade, intracoronary injections of hydralazine failed to induce an increase in myocardial contractile force or heart rate.

To exclude possible inotropic effects of preservatives included in the commercially available preparation of hydralazine, the drug in pure chemical form was dissolved in normal saline solution and injected into the coronary artery both before and after propranolol. The results were the same with the pure drug as with the commercial preparation.

Discussion

Our results indicate that the cardiostimulatory effect of hydralazine is due not only to reflex activation of the sympathetic nervous system but also to direct inotropic and chronotropic action on the myocardium. The evidence supporting such a direct action of hydralazine on the myocardium includes the following:

1. Intravenous injection of hydralazine in the anesthetized dog resulted in an immediate increase in contractile force and heart rate before any reduction in arterial pressure. By contrast, infusion of sodium nitroprusside, another vasodilator drug, did not increase myocardial contractility or heart rate until a well defined decrease in arterial pressure had occurred. Furthermore, with sodium nitroprusside the degree of increase in heart rate and contractility was linearly related to the extent of the decrease in blood pressure, including the initial changes, which was not the case with the initial effects of hydralazine.

2. Intracoronary injection of hydralazine increased contractility in the perfused myocardium without any change in blood pressure, heart rate or the contractile state of the unperfused myocardium. On the other hand, intracoronary injection of sodium nitroprusside did not induce any change in contractility or heart rate until the dose was increased to the point where a systemic hypotensive effect occurred. While caution always is advisable in extrapolating data obtained in anesthetized animals directly to man, the differences observed between the two vasodilators, hydralazine and sodium nitroprusside, were so marked it seems doubtful that they could have been due to the experimental conditions.

Direct cardiostimulatory or inotropic effects of hydralazine: Studies in man of the hemodynamic effects of hydralazine fail to indicate a correlation between the degree of rise in cardiac output and the extent of blood pressure reduction.[2] The hyperdynamic circulatory state found by several investigators[7,9] has been attributed to reflex sympathetic responses to the fall in arterial pressure. Using right ventricular papillary muscles and left atrial muscle strips of kittens, Koch-Weser[10] found that only concentrations of hydralazine far above the therapeutic range produced direct ino-

tropic effects. He concluded that in therapeutic doses hydralazine does not exert a direct inotropic effect. However, because of the greatly different experimental conditions these in vitro results may not be representative of those that would be obtained in vivo. Furthermore, in contradiction to Koch-Weser, Gershwin and Smith[8] demonstrated a direct inotropic effect of hydralazine in isolated guinea pig atria. It is not clear whether the discrepancies between these results and those of Koch-Weser are due to species differences or to other factors. Gershwin and Smith further observed that the inotropic effect was blocked by propranolol as well as by the antihistamines diphenhydramine and tripelennamine. Their results suggest that hydralazine releases histamines, and that this release could in turn set free catecholamines. Such release of catecholamines in the myocardium could then increase myocardial contractility and heart rate.

Nausea, headaches, flushing and circumoral edema have been reported to occur after intravenous administration of hydralazine. These symptoms are consistent with release of histamine. Because intact animals have larger reservoirs of histamine than isolated preparations it is conceivable that in the intact animal therapeutic doses of hydralazine might be capable of releasing histamine and, as a consequence, catecholamines in the myocardium. The observation that propranolol blocks the direct cardiostimulatory effects of hydralazine in our experiment lends further support to this hypothesis. Another possible explanation is that hydralazine is a partial beta adrenergic agonist. Further investigation needs to be done to determine the mechanism of the direct cardiostimulatory effect.

Certain clinical observations also are consistent with the concept that hydralazine exerts local as well as reflex stimulatory effects on the myocardium. For example, hydralazine exerts a greater inotropic effect than other vasodilator drugs.[11] Hydralazine also is more apt to precipitate angina than other vasodilator agents such as sodium nitroprusside.[12] In fact, in patients with acute myocardial infarction administration of sodium nitroprusside often is associated with relief of substernal pain.

Early (direct) versus late (reflex) effects of hydralazine: In this investigation, there seemed to be two distinct phases to the cardiac effects of hydralazine—an early sympathomimetic effect, occurring within 5 minutes of intravenous administration, that was not associated with a significant decrease in blood pressure and a later increased adrenergic effect that was related to the reduction in blood pressure. Thus, our data point to both a direct cardiostimulatory effect of hydralazine that occurs early before the reduction in blood pressure and later additional inotropic and chronotropic effects that appear to be reflex responses as the blood pressure becomes reduced. The evidence for the early direct effect of hydralazine on the myocardium is (1) the appearance of increased contractility before any decrease in blood pressure, and (2) a local increase in myocardial contractility after intracoronary injection of the drug. Neither effect was seen with sodium nitroprusside. It has been suggested that the early effect may be mediated by a local hydralazine-induced release of histamine producing in turn the liberation of catecholamines into the myocardium.

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Effect of Hyaluronidase During the Early Phase of Acute Myocardial Ischemia: An Ultrastructural and Morphometric Analysis

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Hyaluronidase has been shown to reduce the size of experimental myocardial infarcts and to prevent the reduction in collateral coronary blood flow that normally occurs 15 minutes to 6 hours after coronary occlusion. To study the mechanism of action of this agent further, its effects on cardiac ultrastructure during the early phases of myocardial ischemia in the rat were examined. The left coronary artery was ligated for 1 or 3 hours in untreated and hyaluronidase-treated rats and tissue was sampled for electron microscopy. Morphometric analysis, using light microscopy on 1 μ thick specimens of tissue taken from comparable anatomic sites of the ischemic anterior left ventricular wall 3 hours after occlusion, showed that in the untreated rats 80 $\pm$ 7 percent (mean $\pm$ standard error) of myocardial cells and 48 $\pm$ 8 percent of vessels had morphologic evidence of ischemic damage, whereas in treated rats 50 $\pm$ 10 percent of myocardial cells ($P < 0.05$) and 24 $\pm$ 6 percent ($P < 0.05$) of vessels had ischemic changes. Ultrastructural studies of untreated ischemic tissue at 1 hour showed absence of glycogen, nuclear chromatin clumping, intermyofibrillar edema, I bands, intramitochondrial dense bodies and edema, endothelial blebs, gaps and swelling and decreased pinocytotic vesicles, red cell sludging and microscopic foci of hemorrhage. At 3 hours myocardial cell and vascular damage were more severe. In treated animals, more myocardial and endothelial cells from the ischemic anterior ventricular wall appeared normal on electron microscopy at both times. In these animals, myocardial cells that showed ischemic damage had nuclear, mitochondrial and myofibrillar morphologic features similar to those of untreated rats, but more glycogen granules were present than in the untreated group. Hyaluronidase may protect ischemic myocardium by preserving glycogen, and its preservation of collateral flow may be related to its reduction of ischemic damage in the microvasculature.

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Although various interventions have been shown to decrease infarct size after coronary occlusion,[1,2] the precise mechanism of their action is not clear. Several sequential ultrastructural changes occur during the first few hours of acute myocardial ischemia. Alterations occur both in myocardial cells and the microvasculature.[3–5] The use of electron microscopic techniques permits one to determine (1) whether an intervention changes the early morphologic sequence of events that occur after coronary occlusion; (2) whether an intervention protects some organelles selectively and preferentially, or whether the effect of protecting myocardial cells is a generalized one; (3) how soon after coronary occlusion there is evidence of myocardial salvage when an intervention is used; and (4) whether the protective effect of an intervention is directed only at the myocardial cells or at the microvasculature as well. The examination of these events may offer further insight into the mode of action of interventions. Accordingly, this study was carried out to in-

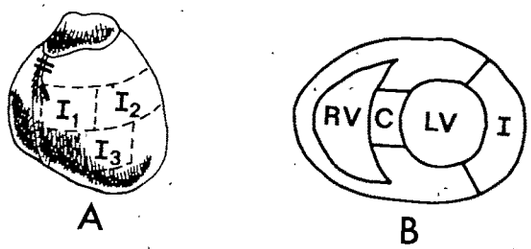


FIGURE 1. A, schematic diagram showing the three ischemic sites sampled for electron microscopy (I_1, I_2, I_3) from the anterior left ventricular wall of the rat heart. **B,** diagram of a transverse section through the rat heart showing the right ventricle (RV), left ventricle (LV), control nonischemic portion of the ventricular septum (C) and ischemic portion of the anterior free wall (I).

vestigate the effect of hyaluronidase on the ultrastructural changes that occur during the early phase of acute myocardial ischemia in the rat. Hyaluronidase was selected because this drug has been shown to decrease myocardial infarct size in dogs,[6,7] rats[8] and, suggestively, in man[9,10] although its mechanism of action has not been defined.

Methods

Albino Charles River male rats, weighing approximately 250 to 300 g were used. Their left main coronary artery was occluded, as described in detail previously.[8] Rats were either untreated (14 rats) or received hyaluronidase (14 rats, 1,500 National Formulary units/kg) by intravenous bolus injection 5 minutes after occlusion. Two rats were submitted to sham operations. After either 1 hour (4 untreated and 4 hyaluronidase-treated rats) or 3 hours (10 untreated and 10 hyaluronidase-treated rats), the animals were reanesthetized and the hearts excised. Just before excision, carbon black (1 mg/kg) was injected intravenously to determine whether a successful occlusion had occurred and to distinguish perfused tissue (black areas) from tissue with reduced coronary flow (pink areas).

Grading of ischemic damage: Transmural sections for electron microscopy were obtained from both the nonischemic midventricular septum and from three sites on the ischemic anterior ventricular wall (Fig. 1). The epicardium and endocardium were trimmed from the muscle. Tissue from each site was cut into six or seven 1 to 2 mm cubes under cold 1 percent osmic acid and allowed to fix for 1 hour in the osmic acid. Two randomly chosen cubes from each of the four sites were then dehydrated in graded alcohol, passed through propylene oxide and a 1:1 mixture of propylene oxide plus Epon 812 overnight before they were embedded in Epon 812. Sections approximately 1 μ thick (that is, thick sections) were stained with toluidine blue for light microscopy. Thin sections were mounted on plain copper grids and stained with aqueous uranyl acetate or lead citrate and examined on a Philips 200 electron microscope. The groups were compared qualitatively using the thin sections and quantitatively using a morphometric technique to evaluate thick sections. The estimate of the percent of injured myocardial and endothelial cells per block of tissue was obtained using a point counting technique with a magnification of 400.[11] If a point on the grid used fell



FIGURE 2. Features of normal and ischemic myocardium from 1 μ thick sections, stained with toluidine blue and viewed with light microscopy (×3,240, reduced by 38 (**A**) and 40 (**B** and **C**) percent). **A,** nonischemic myocardium from the mid ventricular septum. The myocytes show tightly packed sarcomeres. Nuclear chromatin (n) is distributed homogeneously and vessels (**arrows**) appear intact. **B,** untreated ischemic myocardium from the anterior left ventricular free wall after 3 hours of occlusion. Various degrees of myocardial cell edema with vacuoles and separation of myofilaments are present as are nuclear chromatin clumping and margination. Myocardial cells are labeled 1 through 4 depending on the severity of the morphologic changes, as described under Methods. The **inset** shows a type 4 cell that appears entirely vacuolated and architecturally disrupted; contraction bands (cb) are also present. Although rare at 1 hour of permanent ischemia, contraction bands were common by 3 hours of coronary occlusion. Red cell sludging (r) is prominent; intraluminal endothelial blebs (**arrow**) and a microscopic focus of hemorrhage (h) are present. **C,** hyaluronidase-treated ischemic myocardium from the anterior ventricular wall after 3 hours of ischemia. Other than wide I bands (**arrow**) in some myocardial cells, most myocytes and vessels appear normal.

on a myocardial cell, the morphologic severity of the ischemic damage was graded using the following criteria:

0 = normal myocardial cell.
1+ = nuclear chromatin clumping alone, or with occasional vacuoles, plus myocardial relaxation as manifested by I bands.
2+ = the above plus intermyofibrillar edema and more vacuoles.
3+ = the above plus numerous vacuoles or the sarcolemmal membrane lifted off the myofibrils, or both.
4+ = severe swelling and architectural disruption.

When each point falling on a myocardial cell was assigned a numerical value of 0 to 4, a distribution of severity of ischemic damage per section was determined. A mean ischemic score was determined for each rat by calculating the average severity (0 to 4) of myocardial cell injury from the three ischemic sites per rat. Vessels were recorded as being normal or having ischemic changes, including intraluminal blebs, fibrin deposits, red blood cell stasis and localized hemorrhage. The sections were examined by two independent observers who did not know the origin of the specimens. The variability between observers was less than ±3 percent.

Results

Qualitative Appearance

Untreated rats: *Nonischemic myocardium:* Myocardial tissue from sham-operated rats and the nonischemic midventricular septum (which was always perfused with carbon black) of rats with coronary occlusion showed normal myocardial cells and a normal microvasculature (Fig. 2A and 3A).

Ischemic myocardium: After 1 hour of ischemia, tissue from the anterior ventricular wall (unperfused by carbon black and therefore pink) showed the following myocardial cell changes: (1) nuclear chromatin clumping and margination, (2) wide I bands, (3) intermyofibrillar edema, (4) mitochondrial swelling, (5)

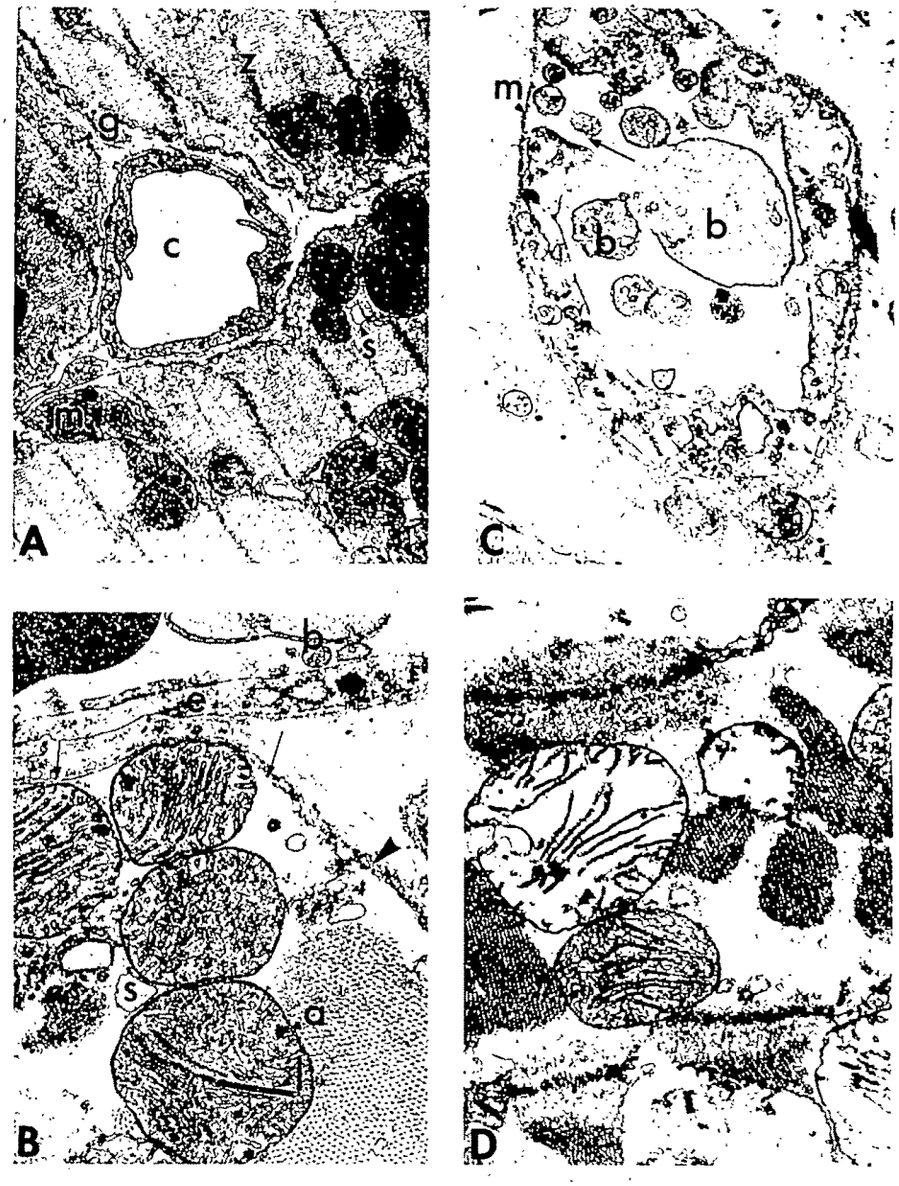


FIGURE 3. Electron micrographs of nonischemic and untreated ischemic myocardium. In this figure and in Figures 4 and 5, all sections were stained with uranyl acetate and lead citrate. **A,** nonischemic myocardium from the midventricular septum (×12,320, reduced by 22 percent.) The sarcomeres are compact and Z bands (Z) in register. Mitochondria (m) show tightly packed cristae, and glycogen (g) is abundant. The capillary endothelial cells (c) in the center contain short intraluminal projections and numerous pinocytotic vesicles. s = sarcoplasmic reticulum. **B,** untreated ischemic myocardium from the anterior ventricular wall after 1 hour of coronary occlusion (×27,600, reduced by 22 percent). The myocardial cell is swollen and the sarcolemmal membrane is discontinuous (**arrows**). The basement membrane of the myocardial cell is intact (**large arrowhead**). The mitochondria show early signs of swelling as manifested by separation of cristae and loss of matrix density. Both amorphous (a) and linear (l) intramitochondrial densities are present. The sarcoplasmic reticulum (s) is swollen and glycogen is absent. The endothelial cell (e) shows loss of pinocytotic vesicles, and a portion of an intraluminal bleb (b) is present. **C,** a capillary after 1 hour of coronary occlusion (untreated) (×17,500, reduced by 22 percent). The endothelial cells show areas of swelling, intraluminal blebs (b) and gaps (**arrow**). m = basement membrane. **D,** untreated ischemic myocardium after 3 hours of coronary occlusion (×25,000, reduced by 22 percent). Intermyofibrillar edema is more prominent than after 1 hour of occlusion. Many mitochondria are massively swollen with disrupted cristae. Glycogen is sparse.

amorphous and linear intramitochondrial dense bodies, (6) swollen sarcoplasmic reticulum, (7) scarce or absent glycogen, and (8) lifting of the sarcolemmal membranes off the myofilaments (Fig. 3B). After 1 hour of ischemia the microvasculature showed the following changes: (1) pale endothelial cytoplasm with loss of pinocytotic vesicles, (2) localized swelling as manifested by intraluminal membrane-bound blebs and occasionally diffuse swelling (Fig. 3C), (3) red blood cell sludging and, less frequently, (4) intraluminal or extravascular fibrin deposits, (5) platelet thrombi, (6) microscopic foci of hemorrhage, and (7) endothelial gaps. The interstitial space contained faintly dense "proteinaceous" material and myocardial cells often appeared separated by a swollen interstitial space.

After 3 hours of ischemia, myocardial cells showed all the features listed but appeared more swollen (Fig. 2B and 3D). Mitochondrial swelling was more prominent with disruption of cristae. Sarcomeres were out of register and contraction bands were common. Lipid droplets were increased in number. Endothelial changes occurred more frequently than at 1 hour. Endothelial degeneration, vesiculation and foci of hemorrhage were more common. Swollen myocardial cells compressing adjacent capillaries were rarely seen. At 3 hours the interstitial space appeared similar to that at 1 hour.

Hyaluronidase-treated rats: *Nonischemic myocardium:* Myocardial tissue from the nonischemic interventricular septum appeared normal and could not be distinguished from untreated tissue.

Ischemic myocardium: In rats treated with hyaluronidase, more cells from the ischemic anterior left ventricular wall (unperfused by carbon black) appeared either normal or showed only slight swelling both at 1

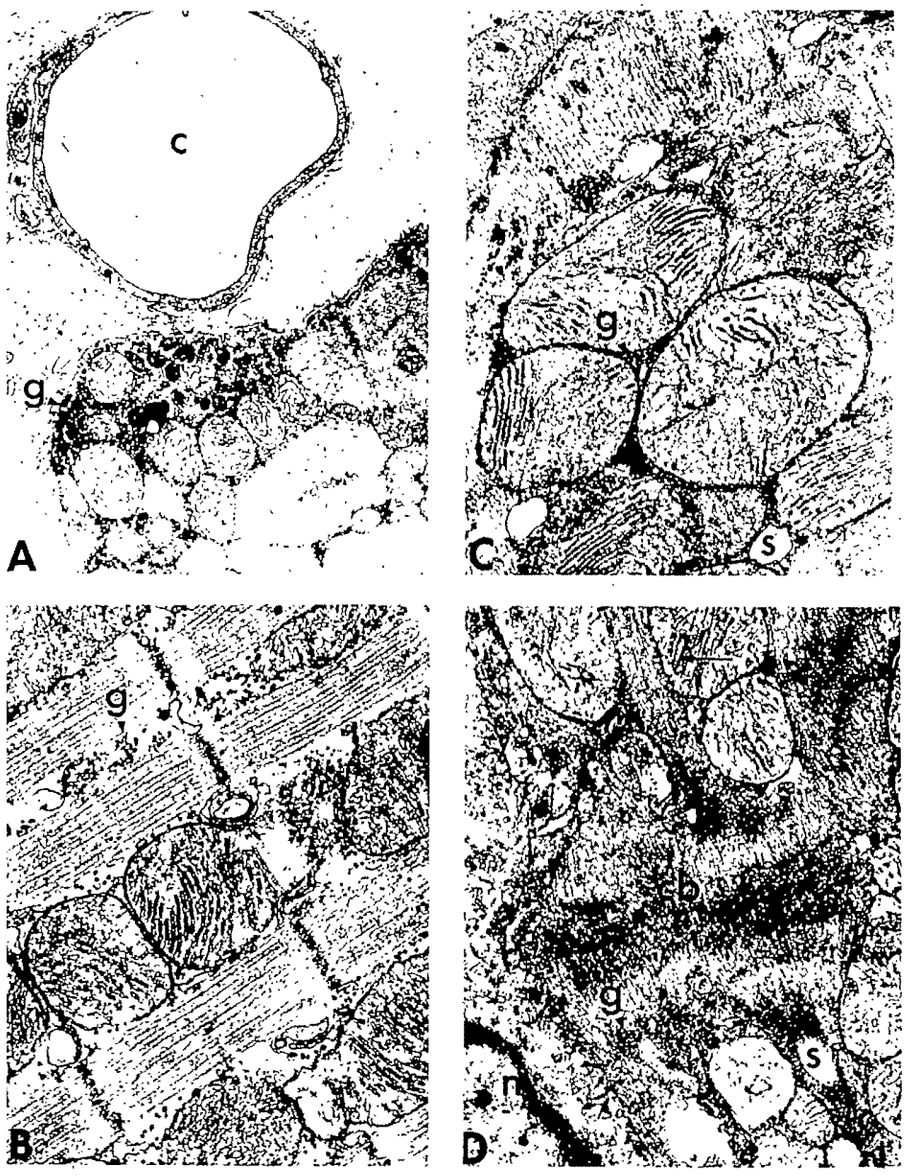


FIGURE 4. Electron micrographs of hyaluronidase-treated ischemic myocardium. **A,** from the anterior ventricular free wall after 1 hour of coronary occlusion (×26,500, reduced by 22 percent). Except for early mitochondrial swelling, the myocardial cell appears intact. Glycogen (g) is abundant. The capillary (c) appears intact. **B,** myocardium after 3 hours of ischemia (×20,000, reduced by 20 percent). Moderate ischemic changes are present including I bands, separation of mitochondrial cristae and early intermyofibrillar edema. Glycogen (g) is present. **C,** myocardium after 3 hours of ischemia (×26,500, reduced by 20 percent). Glycogen (g) is abundant. Early mitochondrial and sarcoplasmic reticular (s) swelling are present. **D,** myocardium after 3 hours of coronary occlusion showing a myocardial cell with severe ischemic changes (×22,600, reduced by 20 percent). Mitochondria are severely swollen and show linear densities (**arrow**). The sarcoplasmic reticulum (s) is swollen. A contraction band (cb) is present and there is nuclear chromatin clumping and margination (n). Despite these changes, glycogen (g) is abundant.

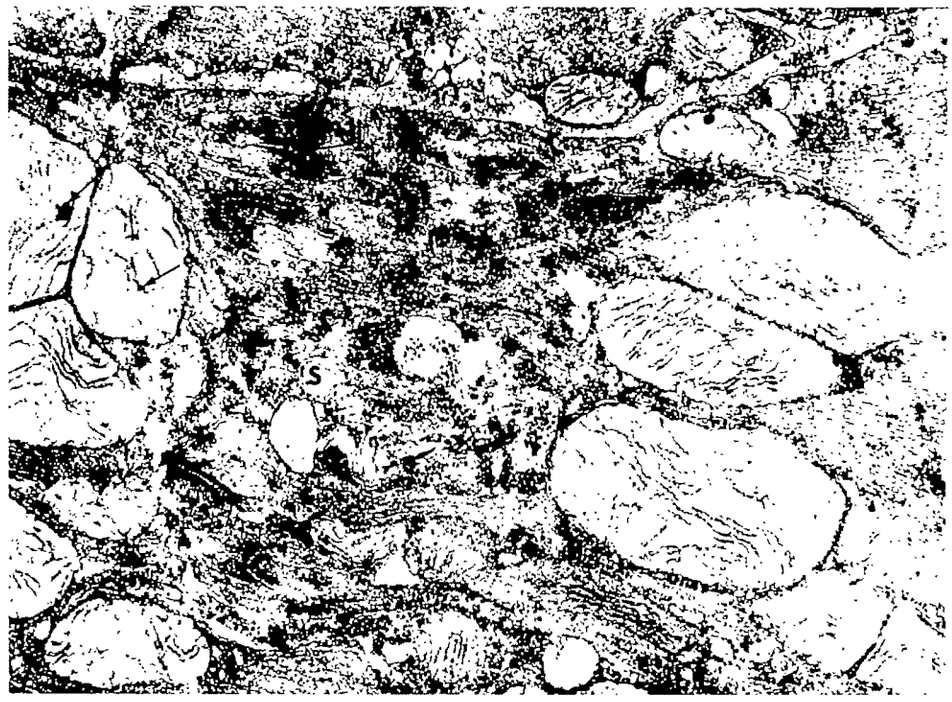


FIGURE 5. Electron micrograph of hyaluronidase-treated myocardium made ischemic for 3 hours, showing a cell with severe ischemic damage (×33,570, reduced by 20 percent). Mitochondria are massively swollen and contain amorphous matrix densities (**arrows**). Sarcoplasmic reticulum (s) is swollen and myofilaments are out of register. The intercalated disc (i) is intact. Glycogen granules are numerous.

and 3 hours on electron microscopy (Fig. 2C and 4, A to C). In cells that showed moderate to severe ischemic injury, the mitochondrial, myofibrillar and nuclear morophologic features appeared similar to those of untreated animals. However, there were numerous glycogen granules, not only in the myocardial cells that appeared normal, but also in many myocardial cells that appeared moderately and severely injured (Fig. 4, A to D and 5) judging by their mitochondria and sarcomeres, a finding not seen in untreated animals. This phenomenon was more striking in rats with 3 hours of ischemia and was present in many, but not all, myocardial cells.

In addition, in rats treated with hyaluronidase, more endothelial cells appeared either normal or had only moderate endothelial swelling on electron microscopy (Fig. 4A). The interstitial space appeared similar to that of untreated animals.

Quantitative Analysis

Results of morphometric analysis of 1 μ thick sections are shown in Table I. In the untreated rats, the percent of myocardial cells showing any degree of ischemic change was similar at 1 (84 ± 10 percent [mean ± standard error] and 3 hours (80 ± 7 percent), but the severity of ischemic changes was greater at 3 hours. In hyaluronidase-treated rats, the percent of myocardial cells showing any ischemic change also was similar at 1 (47 ± 14 percent) and 3 hours (50 ± 10 percent); again the severity of the changes was greater at 3 hours. The mean ischemic score was less in rats treated with hyaluronidase after both 1 hour (1.2 ± 0.1 versus 0.6 ± 0.1,

TABLE I

Morphometric Analysis of Ischemic Myocardial Tissue (mean ± standard error)

	Mean Ischemic Score	Capillaries Showing Change (%)	Myocardial Cells Showing Changes 0 to 4 (%)				
			0	1	2	3	4
1 hour occlusion							
Untreated tissue	1.2 ±0.1	33.5 ±6.0	16.1 ±10.0	66.0 ±11.0	3.2 ±1.8	14.7 ±1.8	0.2 ±0.2
Hyaluronidase-treated tissue	0.6 ±0.1*	32.0 ±7.0	52.6 ±14.1	43.7 ±14.6	1.3 ±0.5	2.4* ±1.4	0 ...
3 hour occlusion							
Untreated tissue	1.6 ±0.2	48.1 ±8.0	20.2 ±7.4	29.6 ±3.8	27.4 ±3.9	21.0 ±4.0	2.0 ±1.1
Hyaluronidase-treated tissue	0.9 ±0.2†	24.0 ±6.0†	49.6† ±10.0	26.0 ±4.4	12.0* ±2.8	12.2 ±5.0	0.2 ±0.2

* = $P < 0.01$, untreated versus hyaluronidase-treated group.
† = $P < 0.005$, untreated versus hyaluronidase-treated group.

$P < 0.05$, in untreated and hyaluronidase-treated rats, respectively) and 3 hours (1.6 ± 0.2 versus 0.9 ± 0.2, $P < 0.005$); 34 ± 6 percent and 32 ± 7 percent of vessels showed ischemic change at 1 hour in the untreated and hyaluronidase-treated groups, respectively. The most common vascular finding in both groups at 1 hour was red cell sludging. At 3 hours there was an increase in the number of vessels showing ischemic change in the untreated group (48 ± 8 percent) but not in the hyaluronidase group (24 ± 6 percent). At 3 hours the qualitative changes of endothelial blebs, fibrin deposits and microscopic foci of hemorrhage were seen more commonly than at 1 hour in both groups.

Discussion

Intravenously administered hyaluronidase was first shown by Oliveira et al.[12] in 1959 to decrease the magnitude of S-T segment elevation in animals and patients with myocardial infarction. They attributed this effect to a decrease in myocardial edema[13] and not to changes in myocardial necrosis. A decade later a number of interventions were shown to be capable of reducing infarct size.[14] Subsequently, hyaluronidase was shown to decrease myocardial infarct size after coronary occlusion as determined with epicardial S-T segment mapping, myocardial creatine kinase (CK) analysis, histologic studies[6] and QRS complex analysis[7] in the dog. Recently, it has been shown by histologic techniques to decrease infarct size in the rat at 48 hours and 3 weeks after coronary occlusion, as determined with myocardial CK studies and morphometric histologic analysis of the entire left ventricle.[8] In addition, precordial mapping techniques in man have shown that hyaluronidase reduces electrocardiographic evidence of myocardial ischemic injury.[9,10]

Mechanisms of hyaluronidase effect on ischemic myocardium: Although the exact mechanism by which hyaluronidase exerts its salutary effect on ischemic myocardium is not known, several hypotheses have been proposed. Because hyaluronidase is an enzyme that is known to depolymerize hyaluronic acid,[15,16] it has been postulated that by depolymerizing mucopolysaccharides in the cardiac interstitium it increases the ability to transport substrate through the extravascular pathway and may augment the supply of glucose and other nutrients to the myocardium. Previous studies using a histologic staining method for hyaluronic acid (Hale's colloidal iron stain) showed that 24 hours after coronary occlusion the quantity of positively stained material was greatly decreased in the interstitial tissue of hearts treated with hyaluronidase.[6] Recently, it was shown that hyaluronidase prevents the reduction in collateral flow that normally occurs in ischemic myocardium 15 minutes to 6 hours after coronary occlusion[17]; therefore, an alternative explanation could be that hyaluronidase is beneficial by providing increased substrate or increased washout of harmful metabolites through improved collateral flow. However, that study did not determine whether the preservation of collateral flow was secondary to decreased myocardial edema or to some direct effect on the microvasculature. In addition, it has been shown that hyaluronidase decreased myocardial edema after coronary occlusion[13] although this decrease in edema could be either a cause of or a consequence of smaller infarct size.

Our findings suggest that hyaluronidase decreases ischemic injury to myocardial cells during the early phase of coronary occlusion, protects the microvasculature and preserves myocardial glycogen granules. Although observations on the reduction of S-T segment elevations suggest that hyaluronidase may be protecting ischemic myocardium as early as 15 minutes after coronary occlusion our investigation provides the first evidence of morphologic preservation during the first few hours of ischemia.

Preservation of myocardial glycogen: An unexpected finding in the hyaluronidase-treated rats was the presence of glycogen granules after 3 hours of coronary occlusion in many myocardial cells that otherwise appeared ischemically damaged. Myocardial glycogen becomes depleted within 1 hour of ischemia[18] or anoxia.[19] In our untreated rats, glycogen granules were nearly entirely absent after 1 hour of occlusion. The preservation of glycogen granules in a population of ischemic cells in the hyaluronidase-treated rats is consistent with the postulate that the drug improves substrate delivery to the myocardium through either improved collateral flow or improved interstitial transport. Theoretically, improved glycogen stores could salvage some reversibly injured ischemic myocardial cells. Why some cells with apparently large glycogen stores still appeared severely injured (Fig. 4D and 5) is not clear. Perhaps anaerobic glycolysis was sufficiently inhibited by metabolites such as lactic acid so that the glycogen, although present, could not be metabolized.[20] Whether hyaluronidase increases the absolute amount of glycogen measured chemically in the ischemic tissue remains to be determined.

Preservation of flow by decreased microvascular damage: Our study also suggests that hyaluronidase may preserve flow by decreasing the microvascular damage that occurs after coronary occlusion. Whereas microvascular damage was commonly seen after 3 hours of ischemia, it was less frequent in hyaluronidase-treated animals. Because swollen myocardial cells compressing adjacent vessels were rarely seen, and capillaries did not appear compressed in areas of interstitial edema, it is doubtful that hyaluronidase prevents a decrease in collateral flow simply by decreasing edema. Whether preservation of collateral flow is the primary mode by which hyaluronidase acts to decrease infarct size is difficult to determine. The fact that some preservation of myocardial cells occurred 1 hour after occlusion, that is, at a time when there was little difference in the amount of vascular change in the two groups of rats, suggests that the preservation of collateral flow may actually be a secondary mode by which hyaluronidase decreases infarct size.

In conclusion, hyaluronidase altered the early morphologic changes that occur after coronary occlusion. Both the myocardial cells and microvasculature were

protected from ischemic damage. The observation that glycogen granules were disproportionately preserved in many myocardial cells supports the theory that hyaluronidase may decrease myocardial infarct size by improving substrate delivery.

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Electrophysiologic Effects of Partial Coronary Occlusion and Reperfusion

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Electrophysiologic changes caused by partial coronary occlusion have not previously been examined. In nine dogs, refractory periods and conduction times were determined using the extrastimulus method after a 50 percent reduction in coronary blood flow. In another five dogs, ventricular automaticity was studied after the production of complete heart block. After 5 minutes of partial coronary occlusion the refractory period in the ischemic zone shortened from 164.6 ± 4.2 (mean ± standard error of the mean) to 149.6 ± 5.8 msec ($P < 0.001$); after 60 minutes it shortened further to 142.5 ± 5.6 msec, resulting in a dispersion of refractoriness. Intramyocardial conduction time from the ischemic to the nonischemic zone was prolonged from 48.6 ± 1.6 to 60.0 ± 3.3 msec ($P < 0.01$), whereas conduction time from the nonischemic to the ischemic zone remained unchanged. No significant changes were observed in ventricular automaticity after partial coronary occlusion (idioventricular rate 56.0 ± 6.4 versus 51.2 ± 6.6 beats/min). Reperfusion 1 hour after partial occlusion resulted in a return of the refractory period and conduction time to preocclusion values, but there were no changes in idioventricular rate. Thus, after a 50 percent reduction in coronary blood flow, the decrease in local refractory period and prolongation of conduction time result in underlying electrical instability predisposing to reentrant arrhythmias whereas automaticity is unchanged. These abnormalities are fully abolished when reperfusion is instituted after 60 minutes of partial coronary occlusion.

Electrophysiologic mechanisms involved in the occurrence of ventricular arrhythmias after experimental total coronary occlusion have been extensively studied.[1–5] However, sudden death presumably due to ventricular fibrillation[6] frequently occurs in patients with only partial coronary obstruction at necropsy.[7–11] Possible mechanisms for this finding may involve electrophysiologic abnormalities produced by either transient occlusion of a coronary artery or sudden restoration of blood flow after such occlusion. A recent study from our laboratory documented electrophysiologic abnormalities after both total coronary occlusion and reperfusion,[5] but the precise nature of electrical instability caused by a partial reduction in coronary flow and subsequent reperfusion has not previously been studied. This investigation was undertaken to examine the electrophysiologic effects of partial coronary occlusion and reperfusion.

Methods

Studies were carried out in 14 dogs weighing 25 to 32 kg. Pentobarbital anesthesia (30 mg/kg body weight intravenously) was administered and the animals were ventilated with room air using a Harvard respirator and a cuffed endotracheal tube. After a left lateral thoracotomy was performed through the fifth intercostal space the heart was suspended in a pericardial cradle.

Instrumentation: The left anterior descending or the main circumflex coronary artery was isolated 2 to 3 cm distal to its origin. Transient ischemia was

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produced by obstructing the artery momentarily while local electrograms were recorded to define potentially ischemic and nonischemic zones both anatomically and by presence or absence of S-T segment elevations in epicardial electrograms. The location of these zones was confirmed with use of methylene blue at the end of each experiment.[12–14] Coronary blood flow was measured with an electromagnetic flow probe (Micron Instrument MU1001-B). The flow probe was selected to fit the diastolic diameter of the coronary artery. Zero flow references were obtained by transiently occluding the vessel. No variation in zero baseline was noted over the course of the experiments.

Four pairs of fine Teflon®-coated stainless steel plunge electrodes (0.003 inch [0.008 cm] in diameter) were inserted deep into the left ventricular myocardium, so as to lodge in the endocardial layer. This placement was confirmed by sectioning the myocardium at the end of each experiment. Two electrodes each were placed in the nonischemic and the potentially ischemic zone. The electrodes constituting each pair were placed 1 mm apart. In each zone, the pair of sensing electrodes was placed 5 to 8 mm from the pair of stimulating electrodes.[5,15] Bipolar electrograms (frequency response 40 to 500 hertz) from the intramyocardial electrodes, standard electrocardiographic lead II and blood pressure (determined with use of a catheter introduced through the carotid artery to the aorta and a P23 Db transducer) were simultaneously recorded using an Electronics for Medicine oscilloscopic recorder at paper speeds of 25 and 100 mm/sec. The following electrophysiologic variables were measured:

Assessment of refractoriness: Refractory periods were determined in nine dogs using the extrastimulus method by scanning the R-R interval at progressively earlier 5 msec decrements using a stimulus with an intensity of twice diastolic threshold and a duration of 2 msec delivered every eight basic cycles. The intensity of the stimulus was kept constant throughout the experiment. The refractory period was defined as the longest R to stimulus interval that did not result in a propagated response (Fig. 1). Because in most experiments there were minor differences between refractory periods in the nonischemic and the potentially ischemic zone during control measurements, absolute as well as relative changes in refractory periods were determined and compared using the following formula:

$$\%\ \text{refractory period} = \left(\frac{\text{refractory period 2 minus refractory period 1}}{\text{refractory period 1}}\right) \times 100$$

where refractory periods 1 and 2 refer, respectively, to measurements during the control period and after both partial occlusion and reperfusion.[5]

Assessment of conduction: Intramyocardial conduction times were determined by measuring the interval from the onset of the impulse in one zone to the onset of the electrogram in another zone (Fig. 1).[15–17] During stimulation of the ischemic zone, the time interval from the onset of the impulse from this zone to the onset of the electrogram in the nonischemic zone was considered ischemic to nonischemic conduction time. When the nonischemic zone was stimulated, the time interval from the impulse to the onset of the electrogram in the ischemic zone was considered nonischemic to ischemic conduction time.

After control recordings of refractory periods and conduction times were obtained, the coronary artery was partially occluded with a rubber-covered adjustable clamp until coronary blood flow was reduced to approximately 50 percent of the control level (mean ± standard error of the mean 50.2 ± 1.8 percent). Measurements of refractory periods and conduction times were carried out for up to 1 hour of partial coronary occlusion at intervals of 5, 15, 30, 45 and 60 minutes. At 60 minutes, the clamp was removed and measurements were taken 15 minutes after reperfusion.

Assessment of ventricular automaticity: In another five dogs complete heart block was produced by injecting 0.2 to 0.4 ml of formaldehyde into the area of the bundle of His.[5,15,18] The rate of the idioventricular pacemaker was determined before and 15 minutes after partial coronary occlusion and after reperfusion and was used as an index of ventricular automaticity.[5,15,18]

Each dog served as its own control and statistical significance was determined using Student's t test for paired values.

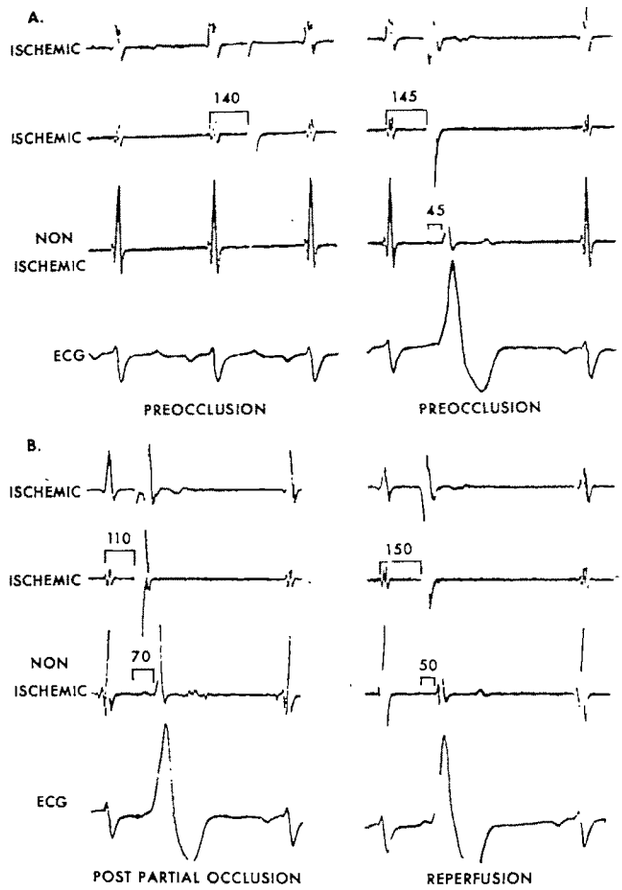


FIGURE 1. A, measurement of refractory periods and conduction times. The test stimulus is started late in the cardiac cycle and moved progressively earlier at 5 msec intervals. At a coupling interval of 145 msec there is a propagated response (seen as a premature ventricular complex in the electrocardiogram [ECG]), but at a coupling interval of 140 msec there is no propagated response, thus indicating the refractory period in the ischemic area. Conduction time is measured from the beginning of the test stimulus in one zone to the onset of the electrogram in the other zone. In this instance, with a test stimulus applied to the ischemic zone, the time interval between the stimulus and the onset of the electrogram in the nonischemic zone (45 msec) was termed ischemic to nonischemic conduction time. **B,** after partial coronary occlusion, the refractory period is shortened from 140 msec to less than 110 msec and the ischemic to nonischemic conduction time is lengthened from 45 to 70 msec. After reperfusion, both the refractory period and conduction time return to control.

TABLE I

Refractory Periods During Partial Coronary Occlusion and After Reperfusion

	Preocclusion Control	After Partial Occlusion					After 15 Min of Reperfusion
		5 Min	15 Min	30 Min	45 Min	60 Min	
Nonischemic zone	164.6 ±4.5	163.7 ±4.5	162.3 ±4.7	158.3 ±4.7	166.5 ±5.7	164.3 ±6.0	166.4 ±5.0
Ischemic zone	164.6 ±4.2	149.6* ±5.8	147.9* ±6.2	142.0* ±6.1	145.0* ±6.5	142.5* ±5.6	166.4 ±5.7

* Significant difference (P [probability] <0.001) from control value.
All measurements expressed in milliseconds (mean ± standard error of the mean).

Results

Refractory periods: Control refractory periods in the nonischemic and potentially ischemic zone were similar (Table I). After partial coronary occlusion, refractory periods in the nonischemic zone remained essentially unchanged (from 164.6 ± 4.5 to 163.7 ± 4.5 msec); in the ischemic zone they shortened by 8.6 ± 2.1 percent (P <0.001) (from 164.6 ± 4.2 to 149.6 ± 6.2 msec), resulting in a dispersion of refractoriness between the two zones. Within 15 minutes of reperfusion, refractory periods of the ischemic zone returned to the control value (Fig. 2).

Intramyocardial conduction: The control conduction time from the ischemic to the nonischemic zone was 48.6 ± 1.6 msec and from the nonischemic to the ischemic zone was 53.2 ± 1.8 msec. Within 5 minutes of partial coronary occlusion, the intramyocardial conduction time from the ischemic to the nonischemic zone was prolonged from 48.6 ± 1.6 to 60.3 ± 3.3 msec (P <0.01). However, conduction from the nonischemic to the ischemic zone was essentially unchanged (53.2 ± 1.8 to 53.9 ± 2.4). All values returned to the control level within 15 minutes of reperfusion (Table II).

Ventricular automaticity: After complete heart block was induced, the mean control rate of the idioventricular pacemaker was 56.0 ± 6.4 beats/min. The ventricular rates remained essentially unchanged after partial coronary occlusion (51.2 ± 6.6 beats/min) and reperfusion (56.7 ± 5.9 beats/min) (Fig. 3).

Discussion

Previous experimental models using acute total coronary occlusion have yielded strong evidence that there is an increased dispersion in refractoriness between the ischemic and the nonischemic zone that provides a setting for reentrant arrhythmias.[3,5,19,20] A prolongation of conduction time in the ischemic zone occurs that also predisposes to reentry.[3,21] Our study demonstrates that a partial reduction in coronary flow results in similar electrophysiologic abnormalities. Beginning within minutes and lasting for the duration of the partial coronary occlusion, there is a significant shortening of refractoriness in the ischemic zone, resulting in an inhomogenity of ventricular refractoriness between the ischemic and the nonischemic zone (Fig. 1, Table I). Moreover, the delay in conduction from the ischemic to the nonischemic zone (Fig. 1) but not in the reverse direction (Table II) could represent unidirectional delay, which would also predispose to reentry.[4]

Because enhanced automaticity, like reentry, is a major cause of tachyarrhythmias,[2,4] we searched for evidence of such enhancement using the complete heart block method.[5,18] Previous studies[3,5,22] have not found that the arrhythmias that immediately follow acute and

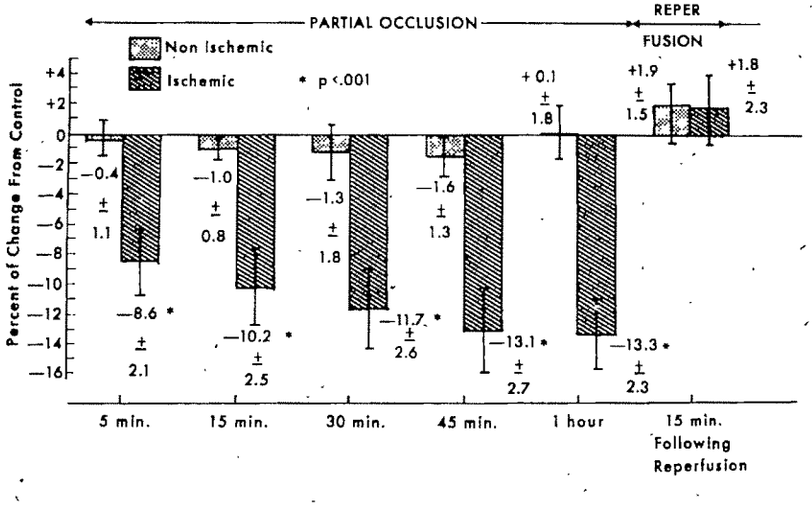


FIGURE 2. Changes in refractory periods after partial coronary occlusion. The refractory period of the ischemic zone is shortened by 8.6 ± 2.1 percent (mean ± standard error of the mean) (P <0.001) in 5 minutes and by 13.3 ± 2.3 percent in 60 minutes. After reperfusion, the refractory period returns to near control levels. No significant change is noted in the refractory periods of the nonischemic zone. p = probability.

TABLE II

Conduction Times During Partial Coronary Occlusion and After Reperfusion

	Preocclusion Control	After Partial Occlusion					After 15 Min of Reperfusion
		5 Min	15 Min	30 Min	45 Min	60 Min	
Nonischemic to ischemic zone	53.2 ±1.8	53.9 ±2.4	54.0 ±3.0	51.8 ±1.3	51.0 ±1.8	53.6 ±2.0	50.7 ±1.4
Ischemic to nonischemic zone	48.6 ±1.6	60.0* ±3.3	61.1* ±2.5	60.0* ±2.8	60.5* ±3.9	61.1* ±2.6	50.7 ±2.3

*Significant difference (P [probability] <0.01) from control value.
All measurements expressed in milliseconds (mean ± standard error of the mean).

complete coronary occlusion are related to enhanced automaticity. Our findings also indicate that ventricular automaticity is not increased immediately after partial coronary occlusion (Fig. 3).

It has been known since the classic experiments of Tennant and Wiggers[23] in the 1930's that reperfusion after total coronary occlusion is intensely arrhythmogenic. Recent electrophysiologic studies have suggested that arrhythmias in this setting may also be explained by dispersion of refractoriness and reentry.[5,24] In our study, when reperfusion followed partial coronary occlusion, the dispersion of refractoriness disappeared (Fig. 2) and ventricular premature complexes were notably infrequent during the reperfusion period.

Clinical implications: These short-term experimental studies have several implications. Many reports have indicated that, although the presumed mechanism of sudden death is a catastrophic arrhythmia,[6] the coronary arteries of patients who die suddenly are usually characterized by incomplete occlusions.[7–11] Our study suggests that even a partial coronary occlusion reducing coronary blood flow by 50 percent results in potentially significant electrical instability. This could predispose to a catastrophic rhythm disturbance that might be unmasked under circumstances of increased myocardial[25] or other[26] stress by means of an additional coronary insult, whether spasm[27] or platelet aggregates.[28]

The electrophysiologic observation relative to reperfusion may also have relevance for aortocoronary saphenous vein bypass surgery. There has been considerable interest in the role of the bypass procedure in the treatment of ventricular arrhythmias.[29–33] In contrast to the previously discussed observation concerning reperfusion after total coronary occlusion,[5] restoration of blood flow after partial coronary obstruction results

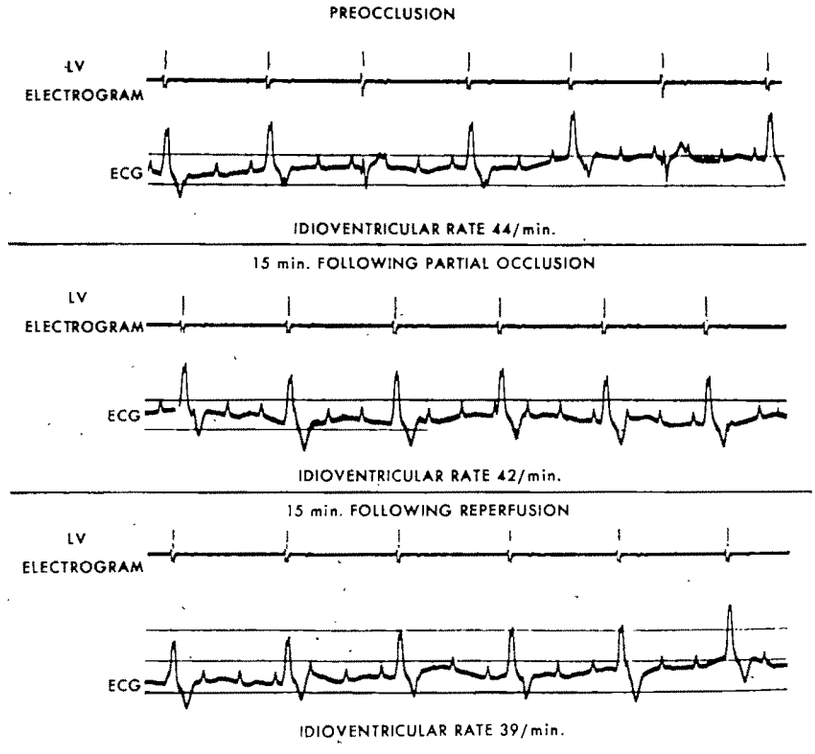


FIGURE 3. Effect of partial coronary occlusion and reperfusion on automaticity. A typical experiment showing the effect of 15 minutes of partial coronary occlusion and reperfusion demonstrating no significant change in the idioventricular rate. ECG = electrocardiogram; LV = left ventricular.

in a normalization of electrical instability. Although our experimental model clearly differs in many important ways from the clinical setting of bypass surgery our data support its potential electrophysiologic role in carefully selected circumstances.

Acknowledgment

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Effects of Pacing-Induced Myocardial Ischemia on Hypoxanthine Efflux From the Human Heart

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Inosine and hypoxanthine are useful markers of early myocardial ischemia in pigs. In this study the applicability of the products of adenosine triphosphate (ATP) breakdown as markers of myocardial ischemia in man was investigated in 25 patients undergoing diagnostic cardiac catheterization for suspected coronary artery disease. Pacing-induced myocardial ischemia resulted in elevated coronary sinus hypoxanthine levels only after the onset of angina in 18 patients (from 1.2 ± 0.2 μmolar [mean ± standard error of the mean] during the control period to 2.4 ± 0.5 μmolar during ischemia, $P < 0.05$), whereas lactate production often occurred before angina was noted. Neither hypoxanthine nor lactate levels changed in seven patients without angina. No significant pacing-induced alterations were found in plasma potassium, inorganic phosphate, glucose or oxygen saturation in either group of patients. No hemodynamic variable, except postpacing left ventricular end-diastolic pressure, served as a useful diagnostic marker separating patients with and without myocardial ischemia. Significant S-T changes during maximal heart rates occurred in only 12 of the 18 patients with angina and in none of those without angina. We conclude that release of hypoxanthine is a useful indicator of pacing-induced ischemia in the human heart.

Protection of the ischemic myocardium with pharmacologic, mechanical or surgical interventions has been a major goal of cardiac research in recent years. Sensitive markers of the degree of ischemia are needed to evaluate the effects of subsequent interventions. Sudden hypoxia at the cell level results within seconds in increased anaerobiosis accompanied by a precipitous decrease in the high energy compound creatine phosphate and followed by a breakdown of adenosine triphosphate (ATP).[1,2] This enhanced degradation of ATP causes increased efflux of the breakdown products that are able to pass the cell membrane—inorganic phosphate, adenosine, inosine and hypoxanthine.[3] In the pig heart a sudden reduction of coronary blood flow is associated with release of myocardial inosine and hypoxanthine[4] that reaches a maximum at 5 minutes of ischemia. Because lactate production reaches its peak value somewhat earlier,[5,6] lactate appears to be preferable as an early metabolic indicator of ischemia and has been used in many clinical studies to quantitate the amount of ischemia. However, its usefulness for this purpose has been questioned[7] because lactate extraction or production patterns may depend on the nutritional status of the patient, the blood levels of free fatty acids and the existence of diabetes mellitus or alkalosis.[8,9] Especially in studies of several hours' duration, in the first hours of myocardial infarction, for example, lactate metabolism may be affected by extracardiac factors. Thus metabolic markers that are less susceptible to extracardiac influences are needed.

Fox et al.[10] have shown that small amounts of adenosine are produced during pacing-induced ischemia in the human heart. However, no experiments have been reported on the release during myocardial ischemia

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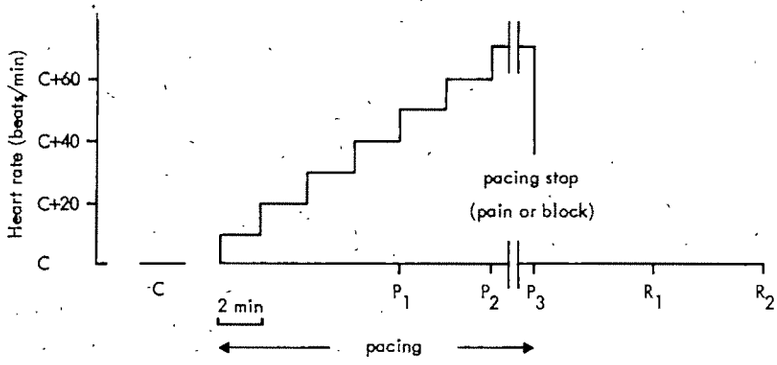


FIGURE 1. The pacing protocol. After control (C) determinations, pacing was started at a rate of 10 beats/min higher than control rhythm. The pacing rate was increased every 2 minutes by 10 beats/min until pacing had to be stopped (because of anginal pain or atrioventricular block). Samples obtained during the control period and during pacing (P_1, P_2 and P_3) and recovery (R_1 and R_2) periods were analyzed.

of the other products of ATP degradation such as inosine and hypoxanthine. We have extended our studies in the pig heart and investigated the release of hypoxanthine during pacing-induced ischemia in the human heart, comparing the possible value of hypoxanthine as an indicator of myocardial ischemia with that of other metabolic, hemodynamic and electrocardiographic variables.

Materials and Methods

Twenty-five adults underwent cardiac catheterization for evaluation of coronary artery disease. In all patients the only manifestation of cardiac disease was angina pectoris for which they were taking nitroglycerin or beta adrenergic blocking drugs. The latter drugs were withheld 1 week before catheterization. No patient had clinical diabetes mellitus. Studies were carried out after an overnight fast and without premedication. No drug, other than 45 to 60 mg of heparin, was administered during the study.

Right heart catherization was performed with a no. 7F Swan-Ganz thermodilution catheter inserted by way of an antecubital vein. Measurements included pulmonary arterial and pulmonary wedge pressures, right ventricular and right atrial pressures and duplicate cardiac output measurements. After the measurements were completed the thermodilution catheter was replaced with a no. 7 bipolar Zucker catheter, which was positioned with its proximal electrode just inside the coronary sinus orifice, where it remained throughout the study. Its position was checked regularly with fluoroscopy.

TABLE I

Summary of Clinical and Catheterization Data

Case no.	Age (yr) & Sex	Site of Old MI	Vessel Involved	Collateral Vessels	LV Contraction	S-T Segment Depression (mv) During Pain
			Group With Angina (no. = 18)			
1	58M	—	LAD, RCA	+	↓	0.2
2	46M	Ant	LAD, LCx	—	↓ Ant	—
3	46M	Inf	LAD, RCA	+	↓ Apex	0.1
4	49M	Post	LAD, LCx, RCA	+	Normal	—
5	49M	—	LAD, LCx, RCA	+	↓ Inf	0.1
6	40M	—	LCx, diag, RCA	—	Normal	—
7	52M	Ant	LAD, LCx, RCA	+	↓ Inf	0.2
8	41M	—	LAD	—	↓ Ant	—
9	56M	Ant, Inf	LMCA, LAD, LCx, RCA	—	↓↓ Apex, Ant	—
10	44M	—	LAD, diag, LCx, RCA	+	Normal	0.1
11	51M	Ant, Inf	LAD, LCx, RCA	+	↓↓ Apex	0.2
12	51M	Inf-Post	LAD, LCx, RCA	—	↓↓↓	0.5
13	38F	—	LAD, marg, LCx, RCA	+	Normal	0.1
14	45M	—	LMCA, LAD, LCx	+	Normal	0.2
15	53M	—	LAD, LCx, RCA	+	↓↓ Apex, Ant	0.1
16	40M	Ant	LAD, LCx, RCA	+	↓↓ Ant	—
17	46F	Ant	LAD	+	↓ Apex	0.2
18	58M	—	LAD, LCx, marg, RCA	+	Normal	0.1
			Group Without Angina (no. = 7)			
19	49M	—	—	—	Normal	—
20	50M	—	—	—	Normal	—
21	42M	Post-Inf	LCx, RCA	—	↓ Inf	—
22	46M	—	—	—	Normal	—
23	34M	—	LAD	—	↓ Apex	—
24	34M	—	—	—	Normal	—
25	40M	—	—	—	Normal	—

Ant = anterior; diag = diagonal branch; Inf = inferior; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; marg = first marginal branch; MI = myocardial infarction; Post = posterior; RCA = right coronary artery.
+ = present; — = absent; ↓, ↓↓, ↓↓↓ indicate increasing degrees of abnormality of the left ventricular contraction pattern.

This catheter was used for atrial pacing and sampling of coronary sinus blood. Through a right brachial arterial cutdown procedure a tip micromanometer catheter (Dallons-Telco MMC no. 8F or Millar Instruments no. 7F) was positioned in the left ventricle for left ventricular pressure recording and sampling of arterial blood.

Pacing procedure: A 15 minute stabilization period was allowed after the catheters were positioned. For control measurements arterial and coronary blood samples were simultaneously drawn, three electrocardiographic leads (I, aVF and V_2), were recorded and left ventricular pressure and its first derivative (dP/dt) were determined. Subsequently atrial pacing was started at a rate 10 beats/min higher than the patient's own control rate. Every 2 minutes the pacing rate was increased by 10 beats/min until patient had anginal pain or the occurrence of atrioventricular (A-V) block made further pacing impossible. Blood samples and hemodynamic and electrocardiographic measurements were taken at 4 minute intervals after the onset of pacing. The last determination during pacing (P_3 in Fig. 1) was always made when cessation of pacing was thought necessary and thus might be obtained within 4 minutes after collection of the previous data (P_2 in Fig. 1). After 5 and 10 minutes of recovery (R_1 and R_2, respectively) these determinations were repeated. Cardiac catheterization was completed with left ventriculography and selective coronary angiography.

Biochemical measurements: Blood (1.5 ml) for hypoxanthine and lactate measurements was rapidly deproteinized with an equal volume of cold 8 percent perchloric acid ($HClO_4$) and centrifuged. In the supernatant, lactate was assayed[11] enzymatically in duplicate on an AutoAnalyzer II (Technicon, Tarrytown, New York). (Standard curves were made with lithium lactate in 4 percent $HClO_4$.) Hypoxanthine was determined according to the method of Olsson.[2] Approximately 2.5 ml of blood was collected for the assay of plasma glucose, potassium and inorganic phosphate[12] on the AutoAnalyzer II with Technicon SMA reference serum/creatine kinase as the standard. Oxygen saturation was determined in duplicate on a hemoreflectometer (American Optical Co., Framingham, Massachusetts).

Hemodynamic measurements: During each recording period left ventricular pressure tracings of 12 successive beats were used to determine left ventricular systolic pressure, left ventricular end-diastolic pressure and maximal rate of rise and decline of left ventricular pressure (maximal and minimal dP/dt, respectively). A modified tension-time index, the product of heart rate and left ventricular systolic pressure, was used as an indication of myocardial oxygen consumption.

Electrocardiogram: S-T segment depression of 0.1 mv or more was considered indicative of myocardial ischemia.

Statistical analysis: Values are expressed as mean values ± standard error of the mean. Comparisons between the different periods were evaluated in each patient using Student's t test for paired data (two-tailed). The significance of differences between the groups with and without angina was determined using Student's t test for unpaired data. A value of $P > 0.05$ was considered not significant.

Results

In 18 of the 25 patients studied, atrial pacing was discontinued because of progressive chest pain (group with angina, Table I). All 18 of these patients had significant obstruction (more than 50 percent of luminal diameter) in one or more coronary vessels; none had single right coronary artery disease. Left ventriculography (single plane determinations in the right anterior oblique projection) showed hypokinetic or akinetic segments of the left ventricular wall in 10 patients; an aneurysm was observed in 2 others (Cases 3 and 9). No patient had mitral insufficiency. In the seven patients without angina pacing was stopped before angina developed because of the occurrence of A-V block. One of the seven (Case 21) had significant two vessel disease and one (Case 23) had one vessel disease. The remaining five patients had a slight narrowing (25 to 50 percent) of one or more vessels. The pattern of ventricular contraction was abnormal in the two patients with significant vessel disease and normal in the other five. Thus,

TABLE II

Hemodynamic Data During Atrial Pacing and Recovery (mean ± standard error of the mean)

	HR	LVSP	TTI X 10^{-3}	LVEDP	LV dP/dt max	LV dP/dt min
			Group With Angina (no. = 18)			
C	78 ± 4	134 ± 4	10.5 ± 0.6	13.4 ± 1.3	1560 ± 50	1720 ± 120
P_1	110 ± 11	123 ± 10	14.5 ± 0.7	7.0 ± 1.0‡	1810 ± 80*	1980 ± 160*
P_2	123 ± 5	130 ± 4	15.8 ± 1.0	9.7 ± 1.9‡	1840 ± 80*	1880 ± 160
P_3	133 ± 4	131 ± 5	17.1 ± 0.8	12.0 ± 2.0	1910 ± 110*	1820 ± 160
R_1	77 ± 4	134 ± 5	10.3 ± 0.7	11.8 ± 1.5	1630 ± 90	1680 ± 140
R_2	77 ± 5	136 ± 4	10.3 ± 0.7	12.6 ± 1.5	1590 ± 80	1650 ± 140
			Group Without Angina (no. = 7)			
C	70 ± 3	136 ± 8	9.4 ± 0.5	12.3 ± 1.2	1710 ± 150	1790 ± 100
P_1	107 ± 4	129 ± 10	13.2 ± 0.8	5.7 ± 1.8†	1850 ± 170	1810 ± 110
P_2	129 ± 5	126 ± 9	16.0 ± 0.8	5.5 ± 2.4†	2000 ± 200*	1820 ± 120
P_3	143 ± 7	127 ± 12	16.6 ± 1.2	8.7 ± 2.6†	2300 ± 200*	1920 ± 160
R_1	73 ± 4	136 ± 12	9.8 ± 0.6	12.9 ± 2.3	1710 ± 140	1860 ± 130
R_2	75 ± 3	137 ± 12	11.2 ± 1.0	12.6 ± 3.0	1750 ± 140	2000 ± 200

*$P < 0.05$; †$P < 0.02$; ‡$P < 0.001$, versus control.

C = control; HR = heart rate (beats/min); LVdP/dt max and LVdP/dt min = peak positive and negative value of the first derivative of left ventricular pressure (mm Hg/sec); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg); P_1, P_2, P_3 = three levels of pacing rates; R_1, R_2 = recovery, 5 and 10 minutes after cessation of pacing (see Fig. 1); TTI = modified tension-time index (heart rate X left ventricular systolic pressure [mm Hg/min]).

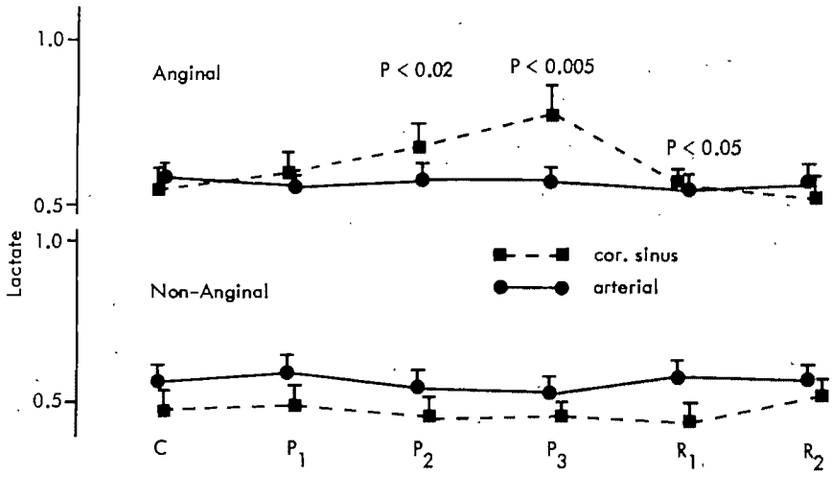


FIGURE 2. Arterial and coronary (cor.) sinus lactate levels (mmolar) during control (C), pacing (P_1,P_2,P_3) and recovery (R_1,R_2) periods. In the group without angina the arteriovenous difference in lactate remained unchanged, whereas in the group in whom pacing was stopped because of angina lactate extraction changed to lactate production. Probability (P) values indicate a significant difference between coronary sinus levels and control values.

these seven patients had less coronary arterial obstruction than the group with angina.

Hemodynamic findings (Table II): There were no significant differences between the groups with and without angina in the control values for any hemodynamic variable. Heart rates in the two groups of patients were similar in each of the three pacing periods. Left ventricular systolic pressure did not change throughout the study. Therefore the changes in the modified tension-time index merely reflect the changes in heart rate. Left ventricular end-diastolic pressure was decreased in both groups during pacing. Immediately after pacing was stopped there was an abrupt increase in left ventricular end-diastolic pressure to values that were different ($P < 0.05$) for the patients with (20 ± 2 mm Hg) and without (12.0 ± 1.6 mm Hg) angina. However, after 5 minutes of recovery, values returned to control level in both groups. Maximal left ventricular dP/dt increased in both groups during pacing. Although the increments were less in the group with angina, the differences were not significant. The maximal rate of decline of left ventricular pressure (minimal dP/dt) remained unchanged in the group without angina but increased during pacing period P_1 in the group with angina (Table II).

Metabolic findings: *Lactate:* Arterial lactate levels were the same in both groups of patients and remained constant throughout the study (Fig. 2, Table III). During the control period there was lactate extraction in both groups. Lactate extraction remained constant throughout the pacing and recovery periods in the 7 patients without angina. In the 18 patients with angina, there was a progressive increase in coronary sinus lactate levels during pacing, giving rise to lactate production in some patients during pacing period P_1. During period P_2 (Fig. 2) coronary sinus lactate levels of the group with angina were significantly elevated when compared with control values, but not when compared with the coronary sinus levels of the patients without angina. However, during angina (P_3) coronary sinus lactate increased to values that were different from those in the group without angina. Recovery values were not different from control values. A relatively large number of patients produced lactate before pain caused a cessation of pacing: Four of the 6 patients with lactate production during P_1 and 7 of the 11 patients who pro-

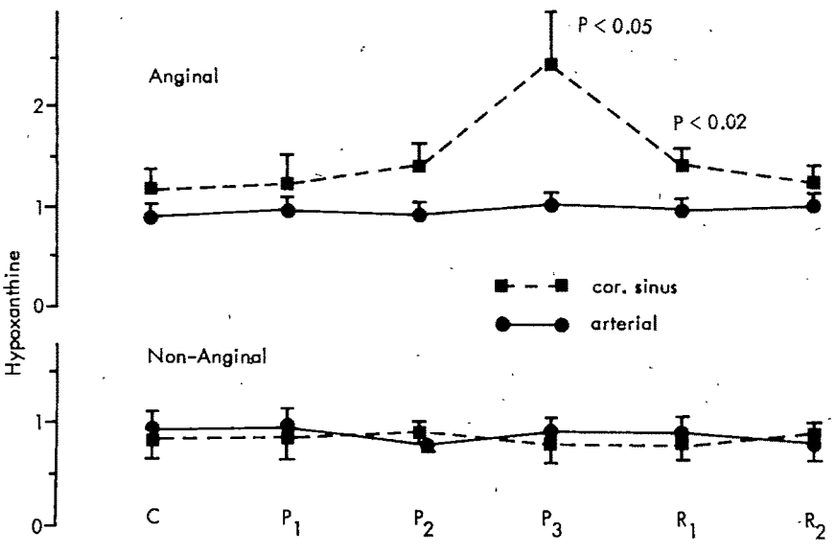


FIGURE 3. Arterial and coronary (cor.) sinus hypoxanthine levels (μmolar) during control (C), pacing (P_1,P_2,P_3) and recovery (R_1,R_2) periods. In the group without angina there were no arteriovenous differences. In the group with angina there was a sharp rise in coronary sinus levels during P_3. Probability (P) values indicate a significant difference between coronary sinus levels and control values.

duced lactate during P_2 were free of pain. The other patients felt some slight discomfort that was not considered severe enough to discontinue pacing.

Hypoxanthine: Arterial levels of hypoxanthine remained unchanged throughout the study in both groups (Fig. 3, Table III). Coronary sinus levels in the group without angina also remained unchanged and did not differ from arterial levels. Consequently no arteriovenous difference in hypoxanthine was observed at any time in the group without angina. By contrast, coronary sinus hypoxanthine concentrations increased gradually during pacing in the group with angina, differing significantly from the control value during the last pacing period (P_3, Fig. 3). At this time the coronary sinus levels in the group with angina were much higher than in the group without angina (2.4 ± 0.5 versus 0.8 ± 0.2 μmolar, respectively, $P < 0.05$). During recovery there was a return toward control levels, although during the first recovery period (R_1) coronary sinus concentrations in the group with angina were still significantly higher than control levels. A large number of patients produced lactate before the occurrence of pain. However, only three patients had elevated coronary sinus hypoxanthine levels (2 μmolar or more) before pain caused cessation of pacing.

Potassium: The arterial potassium levels of both groups showed small but significant fluctuations (Fig. 4). This was especially true for the group without angina, who had significantly elevated levels during pacing. In the group with angina, the fluctuations were less marked and only became significant when the pacing had to be stopped because of pain. In spite of an initial increase in the potassium content of the coronary sinus blood in the group with angina there were no significant differences from the group without angina. Arteriovenous potassium differences did not provide any information that would aid in separating patients with and without angina.

Glucose: In both groups of patients small continuous increases in arterial and coronary sinus levels of glucose

TABLE III

Metabolic Data Obtained in 25 Patients During Atrial Pacing

	Lactate (mmolar)								Hypoxanthine (μmolar)							
	C		P_2		P_3		R_1		C		P_2		P_3		R_1	
Case no.	Art	CS	Art	CS	Art	CS	Art	CS	Art	CS	Art	CS	Art	CS	Art	CS
Group With Angina (no. = 18)																
1	0.42	0.40	0.47	0.41	0.38	0.47	0.42	0.38	1.0	0.9	0.8	0.7	1.0	1.4	0.8	1.3
2	0.40	0.39	0.48	0.52	0.45	0.53	0.48	0.42	1.6	1.6	1.3	1.5	1.2	3.6	1.2	1.8
3	0.36	0.25	0.30	0.37	0.36	0.46	0.25	0.41	1.2	1.2	1.1	1.2	1.2	1.4	1.1	1.8
4	0.53	0.52	0.58	0.50	0.52	0.56	0.58	0.60	1.4	1.5	1.1	1.3	0.5	1.1	1.2	1.3
5	0.71	0.87	0.70	1.01	0.70	1.14	0.71	0.94	1.6	1.1	1.5	1.9	1.5	2.7	1.8	1.8
6	0.75	0.60	0.75	0.72	0.76	0.73	0.75	0.71	1.3	1.5	1.1	1.4	1.4	1.5	1.2	1.5
7	0.61	0.56	0.60	0.59	0.57	0.69	0.48	0.64	0.6	1.3	0.5	1.0	0.8	2.2	0.6	0.9
8	0.52	0.48	0.51	0.53	0.39	0.62	0.46	0.55	0.6	0.9	1.1	0.7	0.8	2.0	0.7	1.6
9	0.68	0.62	0.66	0.64	0.68	0.84	0.64	0.61	0.6	0.8	0.7	0.6	0.6	2.0	0.4	0.8
10	0.54	0.56	0.52	0.55	0.55	0.63	0.54	0.56	0.8	1.1	1.0	1.0	1.1	1.2	1.0	1.1
11	0.57	0.57	0.60	1.15	0.62	1.04	0.62	0.75	0.9	0.6	0.8	1.3	0.9	2.4	1.0	1.3
12	0.98	1.33	1.09	1.53	1.03	1.60	0.98	1.25	1.8	4.0	1.3	2.1	2.3	3.7	1.2	3.7
13	0.50	0.57	0.53	0.66	0.55	0.68	0.48	0.55	1.0	1.3	0.9	1.5	0.9	2.4	0.9	1.4
14	0.47	0.34	0.52	1.21	0.64	1.58	0.60	0.48	0.6	0.5	0.8	3.8	1.2	10.6	1.2	1.8
15	0.47	0.45	0.44	0.47	0.46	0.31	0.47	0.37	0.4	1.1	0.6	1.2	1.0	0.8	0.8	1.0
16	0.99	0.50	—	—	0.89	0.71	0.89	0.42	0.5	0.5	—	—	0.4	1.6	0.5	0.8
17	0.53	0.44	0.68	0.67	0.59	0.74	0.58	0.60	0.8	0.9	0.8	1.2	0.9	1.2	0.7	1.2
18	0.54	0.50	0.54	0.59	0.55	0.71	0.55	0.53	0.6	0.7	1.0	1.6	0.9	1.4	0.7	1.3
Mean	0.58	0.55	0.59	0.71	0.59	0.78	0.58	0.60	1.0	1.2	1.0	1.4	1.0	2.4	0.9	1.5
±SEM	0.04	0.05	0.04	0.07	0.04	0.08	0.04	0.05	0.1	0.2	0.1	0.2	0.1	0.5	0.1	0.2
P value																
vs C			NS	<0.02	NS	<0.005	NS	<0.05			NS	NS	NS	<0.05	NS	<0.02
Art vs CS	NS		<0.05		<0.01		NS		NS		<0.025		<0.02		<0.001	
Group Without Angina (no. = 7)																
19	0.62	0.48	0.60	0.50	0.63	0.50	0.62	0.38	0.7	1.2	0.8	1.1	1.2	1.0	0.8	1.3
20	0.59	0.46	0.57	0.53	0.59	0.54	0.63	0.67	2.0	1.0	1.1	1.3	1.2	1.0	1.2	0.8
21	0.54	0.44	0.59	0.41	0.59	0.37	0.56	0.39	0.6	1.0	0.8	1.4	0.6	0.7	0.8	1.0
22	0.44	0.33	0.47	0.37	0.50	0.46	0.55	0.33	0.6	0.9	0.7	0.9	1.0	1.1	0.8	1.0
23	0.71	0.74	0.76	0.71	0.72	0.70	0.85	0.68	0.2	0.2	0.5	0.2	0.2	0.2	0.2	0.2
24	0.40	0.30	0.33	0.33	0.37	0.35	0.37	0.37	0.9	0.6	0.6	0.8	0.5	0.4	1.0	0.4
25	0.70	0.64	0.68	0.58	0.53	0.54	0.69	0.64	1.3	1.2	1.3	1.2	1.2	1.0	1.3	0.7
Mean	0.57	0.48	0.57	0.49	0.56	0.49	0.61	0.49	0.9	0.9	0.8	1.0	0.8	0.8	0.9	0.7
±SEM	0.05	0.06	0.05	0.05	0.04	0.05	0.06	0.06	0.2	0.2	0.1	0.2	0.2	0.2	0.2	0.0
P value																
vs C			NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Art vs CS	<0.01		<0.01		NS		<0.05		NS		NS		NS		NS	

Art = arterial; C = control heart rate; CS = coronary sinus; NS = not significant; P_2 and P_3 = two levels of pacing rates (see Table I); *P* = probability; R_1 = 5 minutes after cessation of pacing; SEM = standard error of the mean.

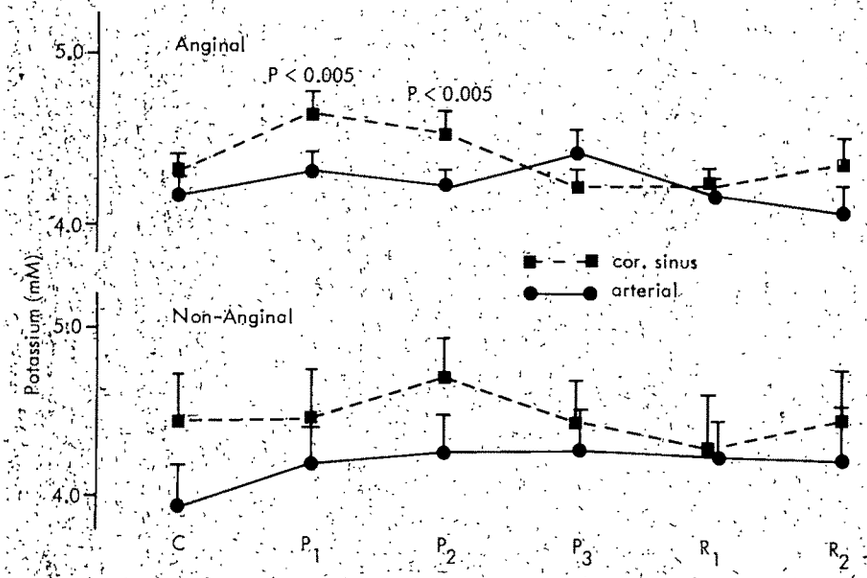


FIGURE 4. Arterial and coronary (cor.) sinus potassium levels during control (C), pacing (P_1,P_2,P_3) and recovery (R_1,R_2) periods. In spite of significant arteriovenous differences in the group with angina, there were never significant differences in the potassium levels of the two groups. Probability (P) values indicate a significant difference between coronary sinus levels and control values.

were found during the pacing and recovery periods (Fig. 5). However, arteriovenous differences remained very small and were not different in the two groups of patients.

Oxygen extraction: This variable remained unchanged for both groups (60 ± 2 percent) throughout the pacing and recovery periods.

Inorganic phosphate: Determinations were carried out in the first eight patients (Fig. 6). No significant changes in inorganic phosphate levels were observed.

Electrocardiographic measurements: No patient in the group without angina had S-T changes during pacing. Twelve of the 18 patients with angina showed S-T segment depression of 0.1 mv or more during pain when values were compared with control values (Table I).

Discussion

This study was designed to determine whether ischemia induced by atrial pacing would result in the release of breakdown products of adenosine triphosphate from the human heart. The production of other metabolites and hemodynamic as well as electrocardiographic alterations were measured. The patients were separated into groups with and without angina; in 18 patients atrial pacing was stopped when angina occurred and in 7 patients it was stopped when A-V block occurred without angina.

Electrocardiographic measurements: S-T changes during atrial pacing have not been proved useful as a discriminant factor[13] in angina. Our study confirms this as only 12 of 18 patients manifested significant S-T segment changes during pain.

Hemodynamics: The hemodynamic findings in our patients compare very well with those reported by others. Maximal pacing heart rates and modified tension-time index values are comparable with those found by others, although heart rates were increased at various intervals.[14–18] Immediately after pacing a significant

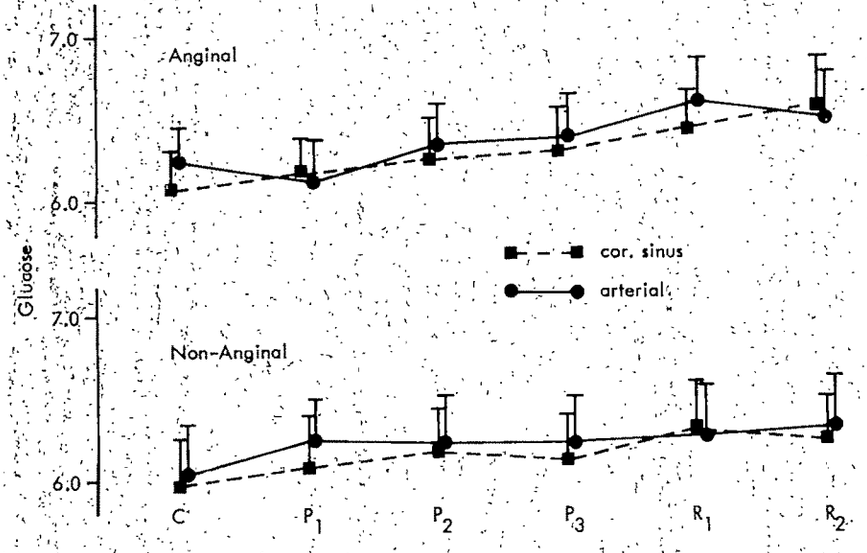
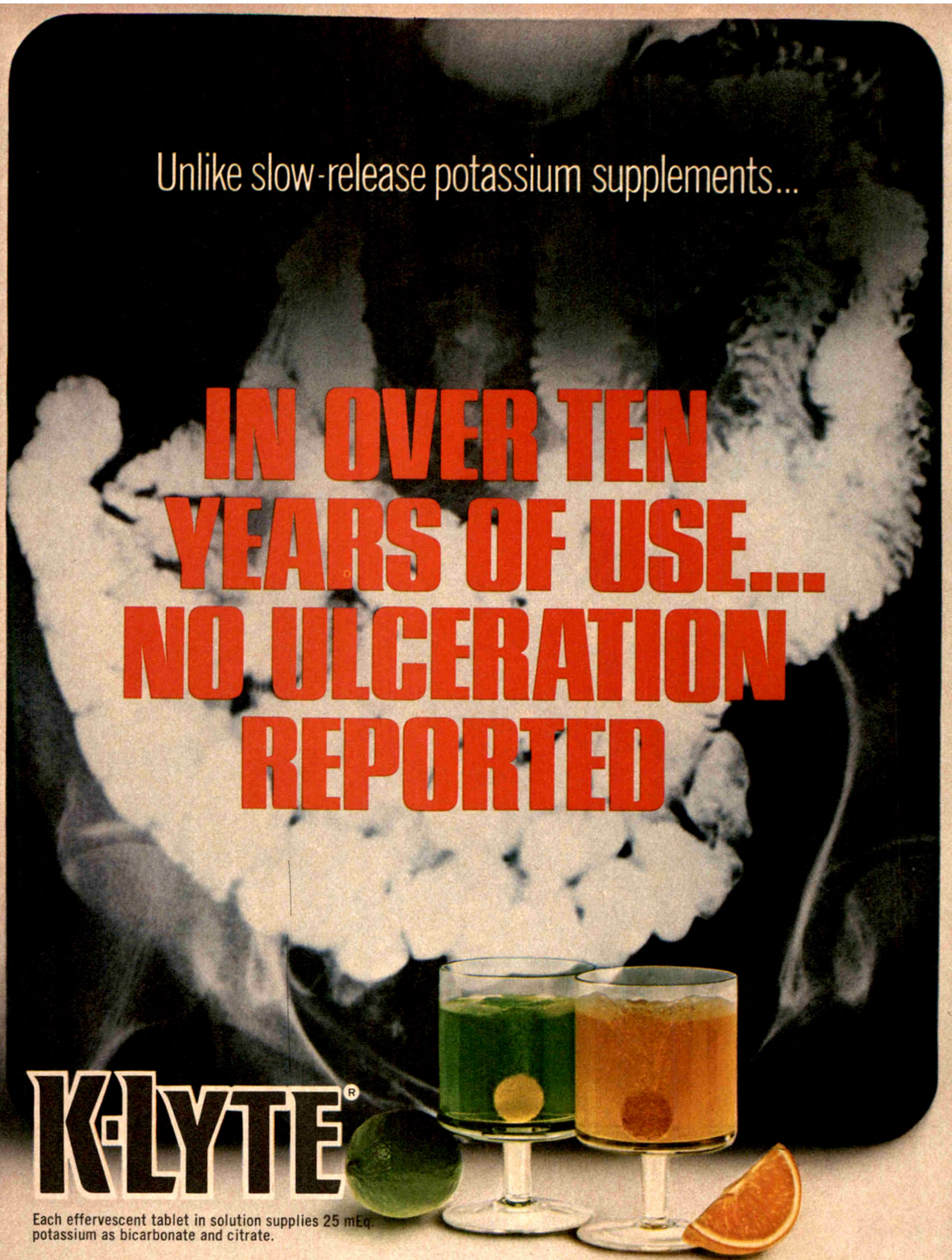


FIGURE 5. Arterial and coronary (cor.) sinus glucose levels (mmolar) during control (C), pacing (P_1,P_2,P_3) and recovery (R_1,R_2) periods.



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Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

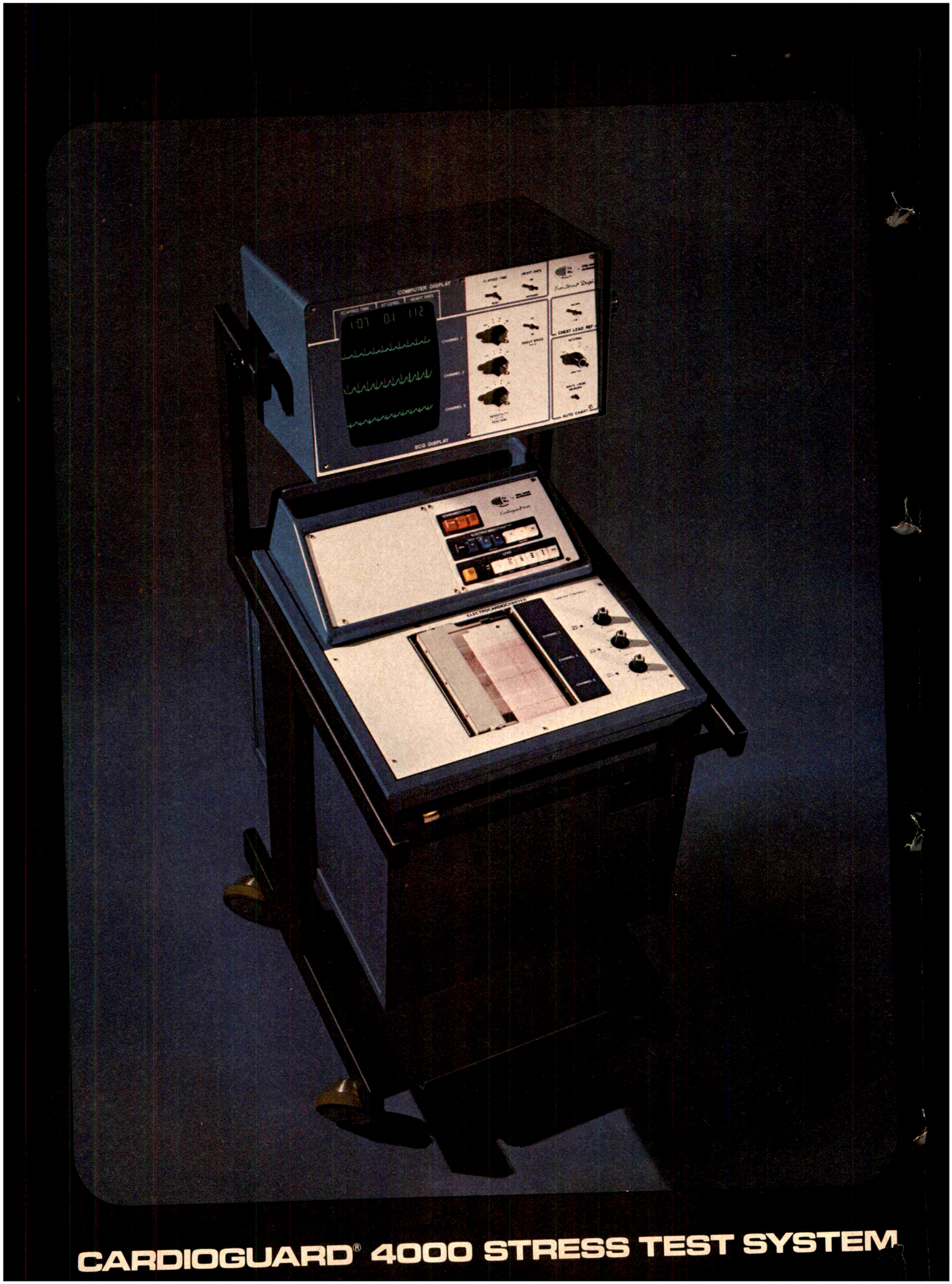
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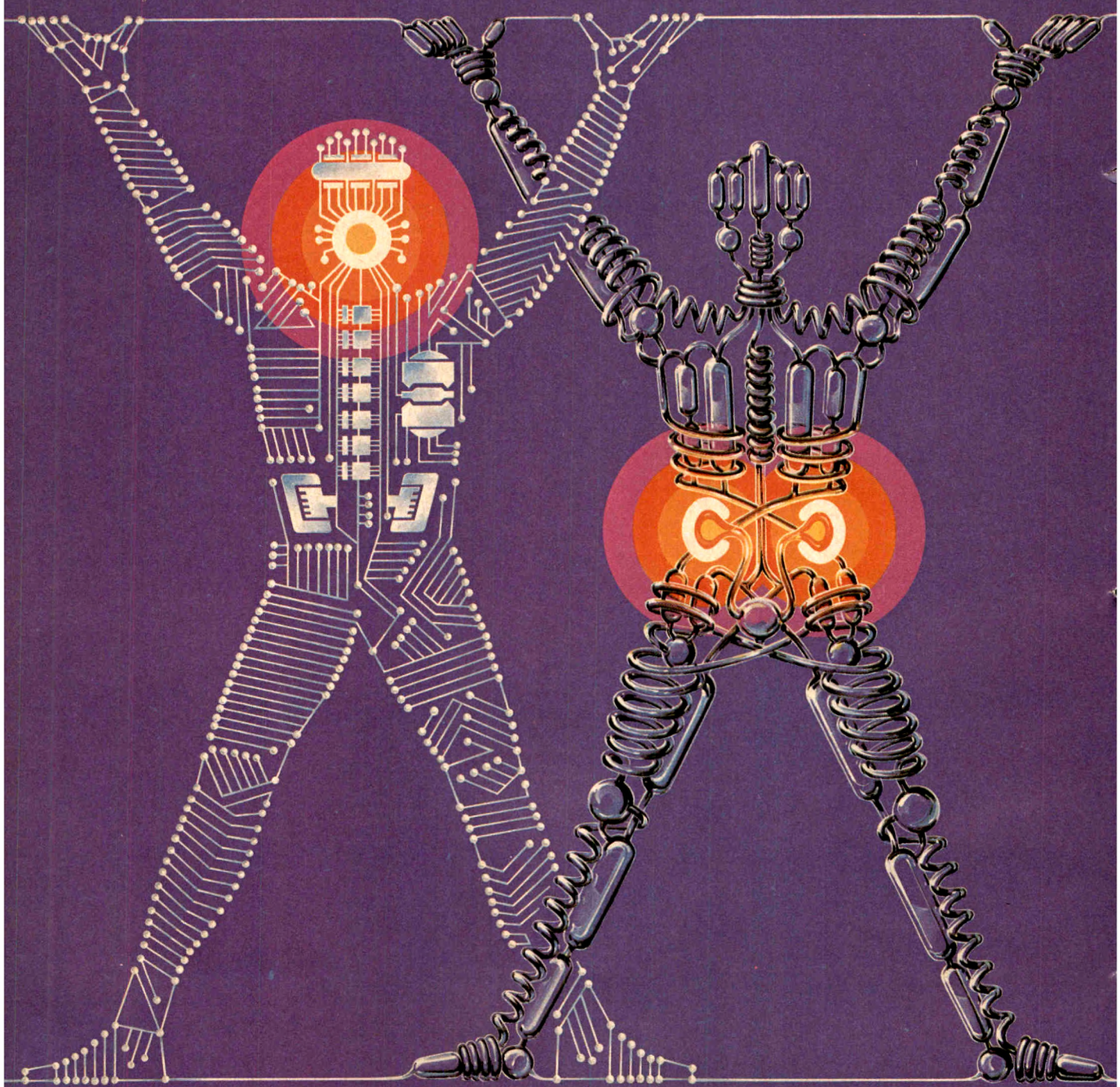
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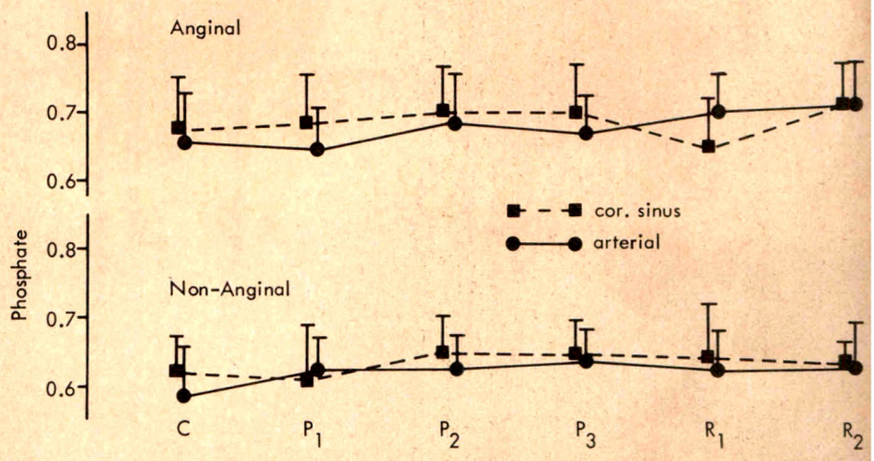


FIGURE 6. Arterial and coronary (cor). sinus inorganic phosphate levels (mmolar). The differences between the groups with and without angina were not significant. Abbreviations as in Figure 5.

difference in left ventricular end-diastolic pressure was observed between patients with and without angina. In the group with angina end-diastolic pressure increased above the control value, whereas in the group without angina it did not differ from the control value. This confirms the findings of others.[14,19] McLaurin et al.[20] reported a decrease in the maximal rate of decline of left ventricular pressure (minimal dP/dt) in patients with angina and suggested that this variable could be used as an index for impaired ventricular relaxation. By contrast, we found no change in minimal dP/dt in patients with or without coronary artery disease; this finding is in agreement with the data of Schwarz et al.[21]

Metabolic markers: *Increases in coronary sinus hypoxanthine concentrations* to values exceeding control up to 20-fold (Table III) were found during anginal pain, whereas there were no appreciable changes in the group without angina. Because arterial levels for both groups remained constant throughout the experiment, hypoxanthine production must have increased during pain in the group with angina. This increased hypoxanthine efflux probably reflects ATP degradation.[2,3] Inosine, although a very good marker of myocardial ischemia in the pig heart,[4–6] was not produced in measurable amounts in this study. Even during ischemia the inosine concentration was less than 0.4 μmolar. This may indicate a quick turnover from adenosine by way of inosine to hypoxanthine.

Adenosine efflux was observed by Fox et al.[10] in coronary sinus blood during pacing-induced ischemia, although the nucleoside usually was not detectable during control situations. Adenosine was a relatively insensitive marker of ischemia (only 10 of their 15 patients had significant differences during angina). In our study only 3 of the 18 patients with angina failed to show increases in venous hypoxanthine levels (more than 0.2 μmolar) during angina. Because the method of Fox et al. for measuring adenosine requires 90 ml of blood compared with only 1.5 ml for hypoxanthine measurements, the latter method is obviously preferable.

The data on lactate metabolism show increased anaerobic glycolysis in the course of atrial pacing in the group with angina. There was extraction during the control period, although somewhat less than in the group without angina because some patients were already producing lactate. During the pacing periods there was progressive lactate production. All but one patient with angina showed significant lactate abnormalities during the last pacing period (P_3). Because this patient (Case 6) also had unchanged venous hypoxanthine levels it is possible that he did not have true angina or that his coronary artery disease lay outside the area sampled by the catheter. He was the only patient in the group with angina who had no significant obstruction in the left anterior descending coronary artery. The presence of abnormal myocardial lactate metabolism before angina suggests that anaerobic glycolysis occurs very early in the course of developing myocardial ischemia and that angina is experienced somewhat later in the process.[13] Significant hypoxanthine production also developed later than lactate production. This finding is in agreement with the results of our experiments in the ischemic pig heart,[5,6] in which sharp increases in local coronary venous nucleoside concentrations were preceded by relatively larger lactate concentrations.

None of the other metabolic variables proved useful in identifying myocardial ischemia. There was no change in oxygen saturation in either group during pacing; this finding has been reported before.[14,22,23] Dagenais et al.[24] found no significant differences in myocardial glucose extraction in patients with and without angina. A difference was found by Most et al.,[25] but they concluded that glucose extraction could not be used as an indicator of myocardial ischemia because of a wide variability in individual subjects. No significant arteriovenous differences in glucose levels were found in our patients, although small but steady increases in arterial and venous levels were observed. The latter increases may have been the result of catecholamine stimulation in response to the stress situation, but it is doubtful that such small increases in glucose concentrations interfered with lactate metabolism in our study.

Inorganic phosphate production by the ischemic myocardium has been reported in dog[26–29] and pig[6] preparations. Changes depended on the extent of myocardial ischemia[27] and were usually small when

mpared with changes in other metabolites.[6] Chiong al.[30] studied the effects of pacing-induced ischemia inorganic phosphate balance of the human myocarum. Small but significant changes were found in lacte producers. However, inorganic phosphate proiction was found in only 55 percent of their patients th angina. In our first eight patients no significant anges could be found (see also Ref 24) and further terminations were not carried out.

Potassium egress induced by atrial pacing from both e nonischemic and (to a greater extent) the ischemic art was reported by Parker et al.[31] They suggested at the negative potassium balance was rate-dependent id apparently aggravated in the presence of myocaral ischemia. Our findings partly support these obrvations because early rises in venous potassium levels curred in both groups, and were more pronounced in e group with evidence of ischemia. Changes in venous potassium were always small and accompanied by similar fluctuations in arterial potassium levels. Thus potassium efflux was an unreliable indicator of myocardial ischemia.

Clinical implications: Abnormal myocardial lactate metabolism occurs early in the course of developing myocardial ischemia. Therefore it remains a very important, but not always necessarily specific, metabolic marker of myocardial ischemia. In these situations the simultaneous measurement of hypoxanthine could provide additional information about abnormal myocardial metabolism.

Acknowledgment

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*Combipres is not indicated for initial therapy of hypertension. It is indicated for hypertensive patients who need more than one drug for adequate lowering of blood pressure and who have proved to be responsive to its components given separately in dosages equivalent to those in the combination.

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase, congestive heart failure, Raynaud's phenomenon, vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

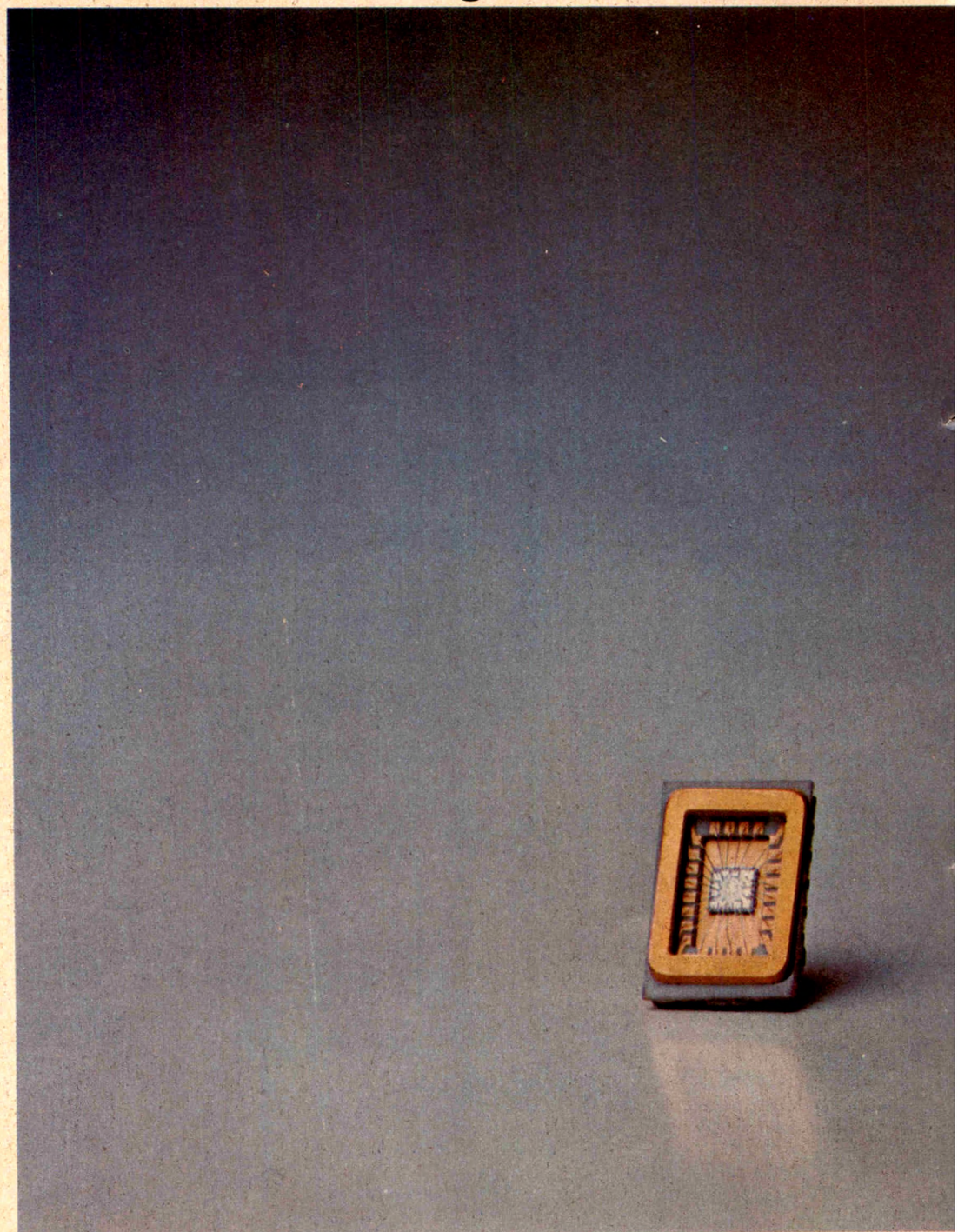
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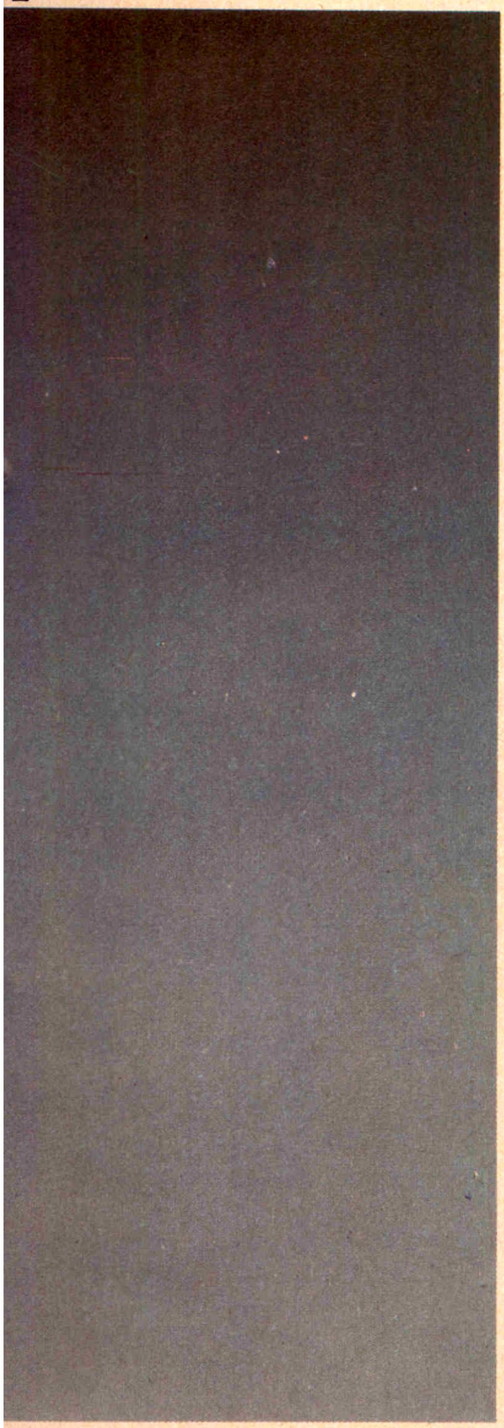
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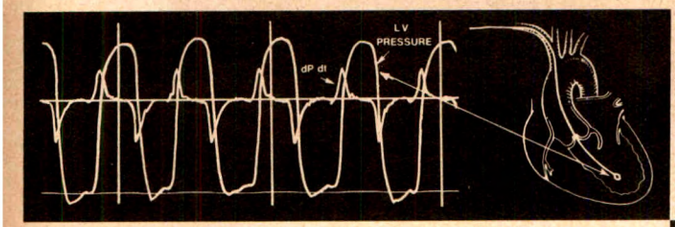
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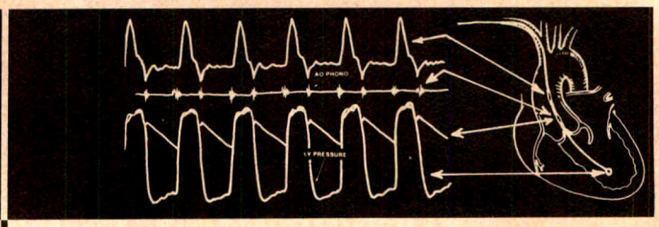
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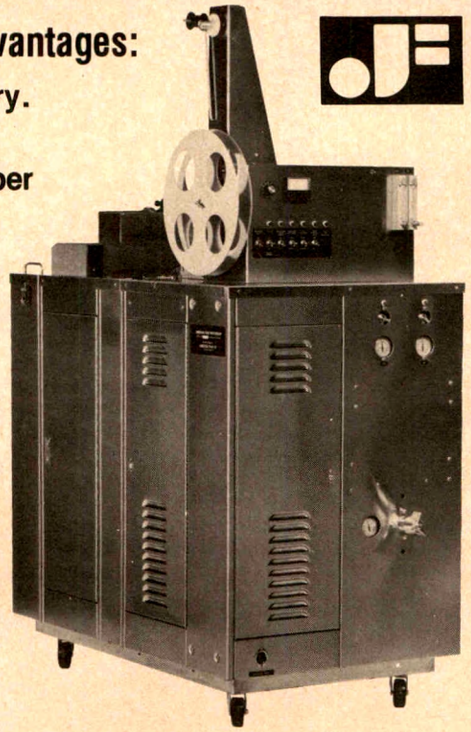
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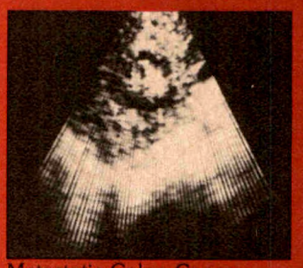
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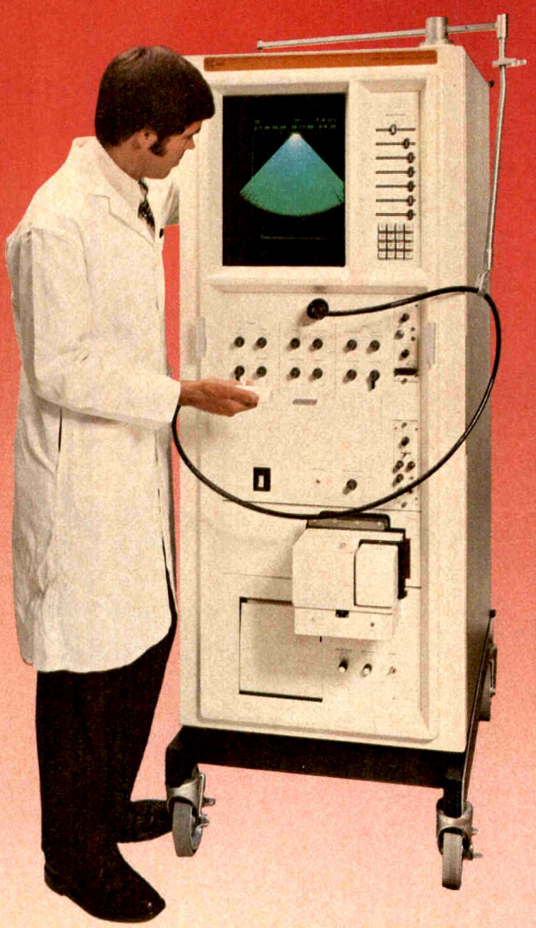


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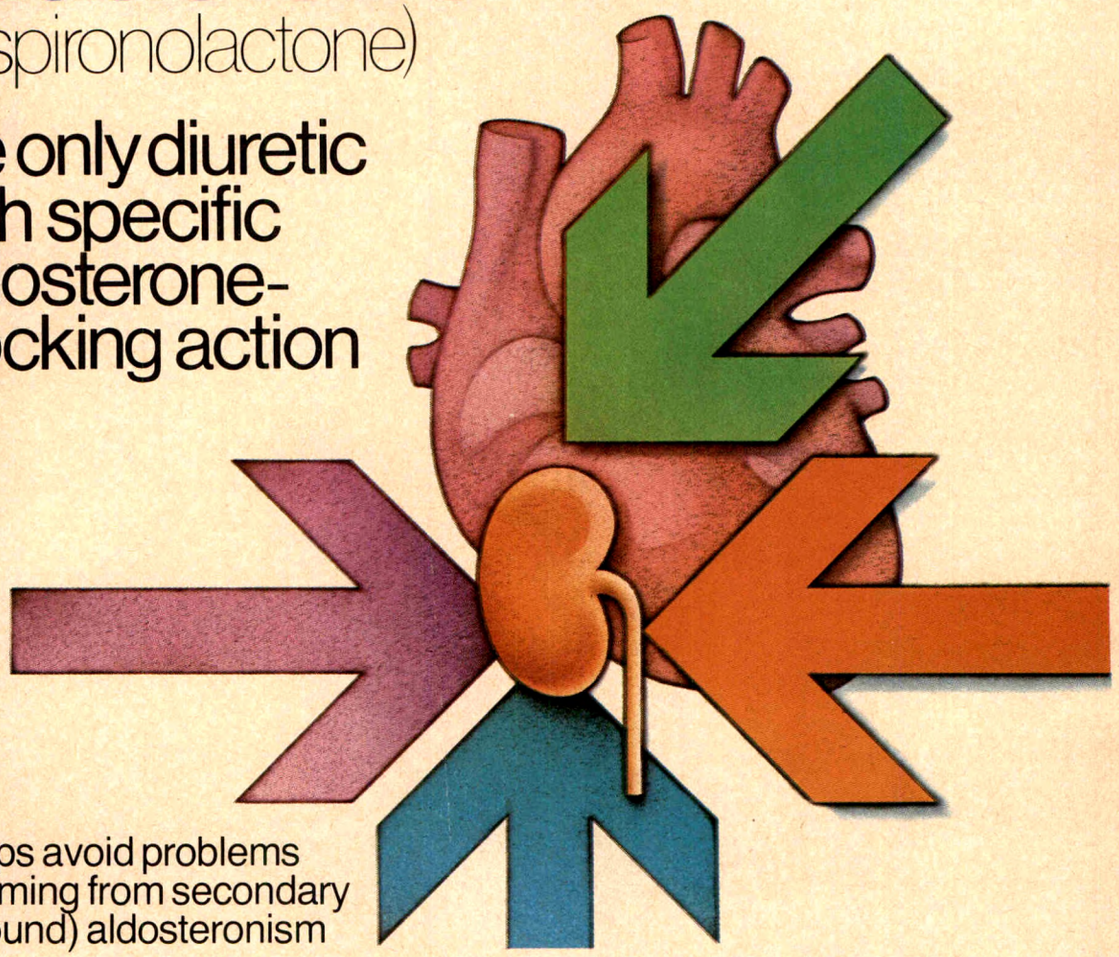
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Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

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   - B. Indomethacin therapy
   - C. Either of the above
   - D. Neither of the above

2. Furosemide is generally not a good anti-hypertensive drug because
   - A. It is too short acting
   - B. It is too long acting
   - C. It is too toxic

3. In a series of 100 positive treadmill tests performed in apparently normal individuals, ten were ultimately shown to be falsely positive. Thus,
   - A. The sensitivity of the test is 90%
   - B. The specificity of the test is 90%
   - C. The relative statistical risk is 90%

4. Isosorbide dinitrate sublingually has been shown to decrease
   - A. After load
   - B. Pre load
   - C. Left ventricular chamber size
   - D. All of the above

ANSWERS:
4. D
3. B
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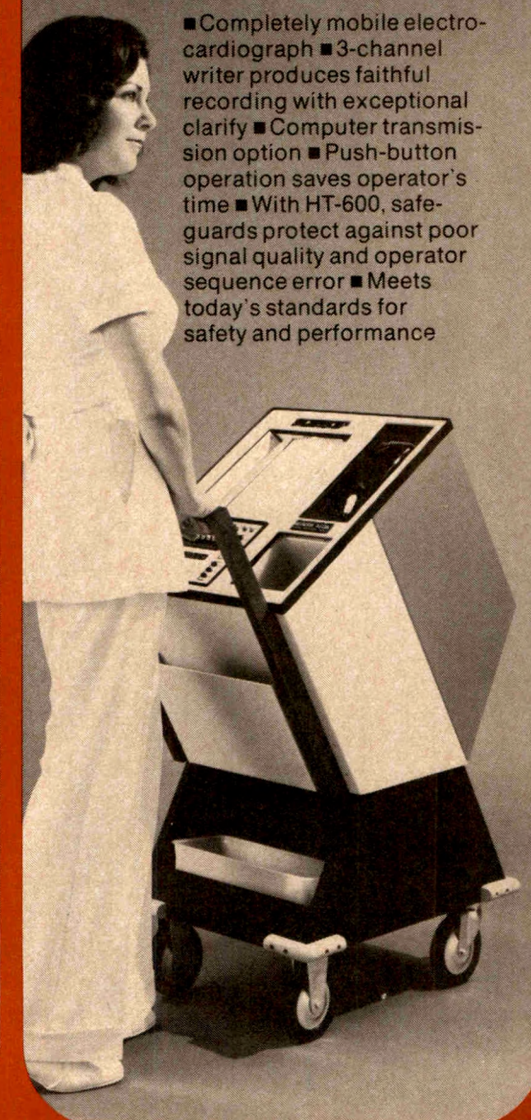
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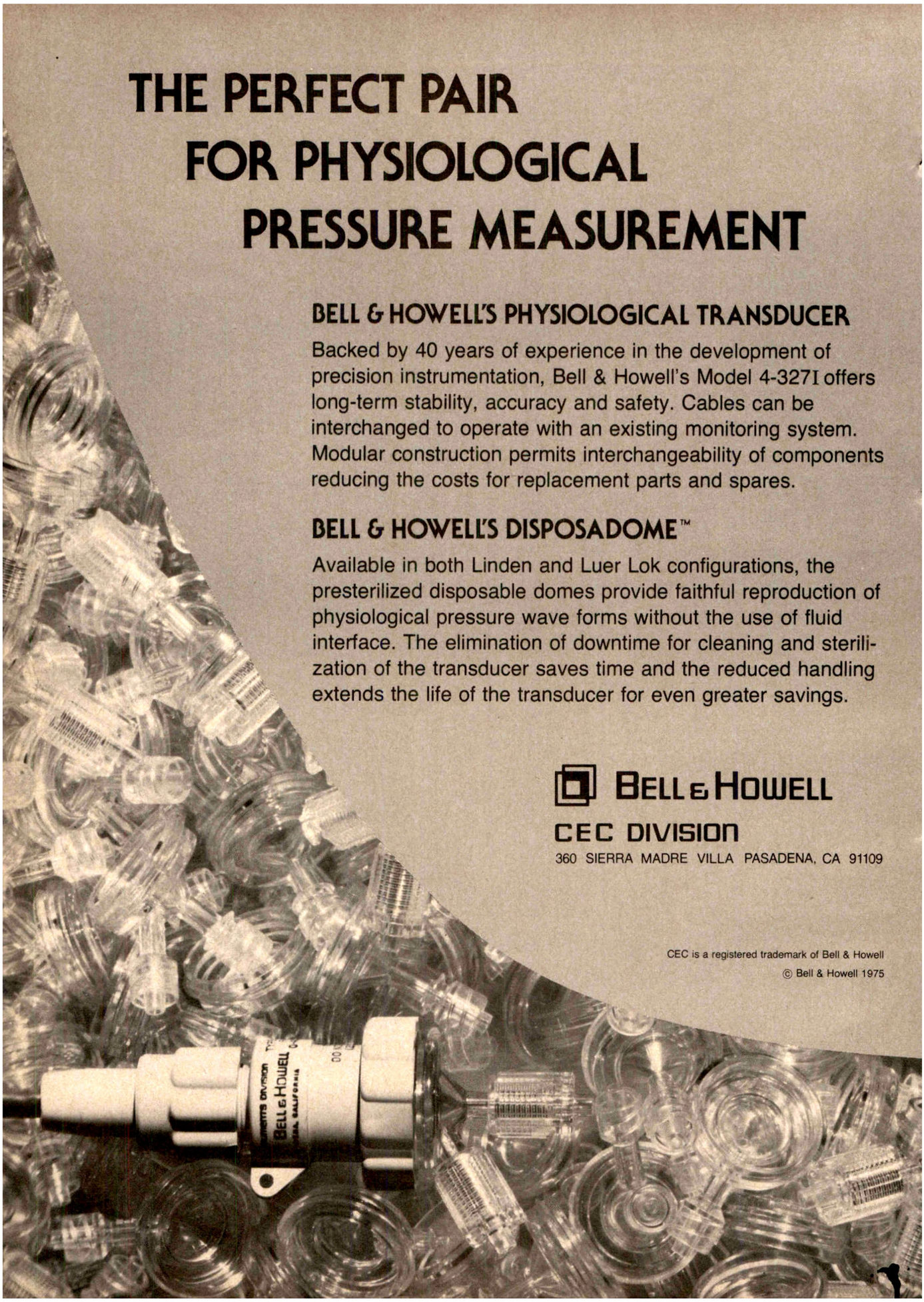


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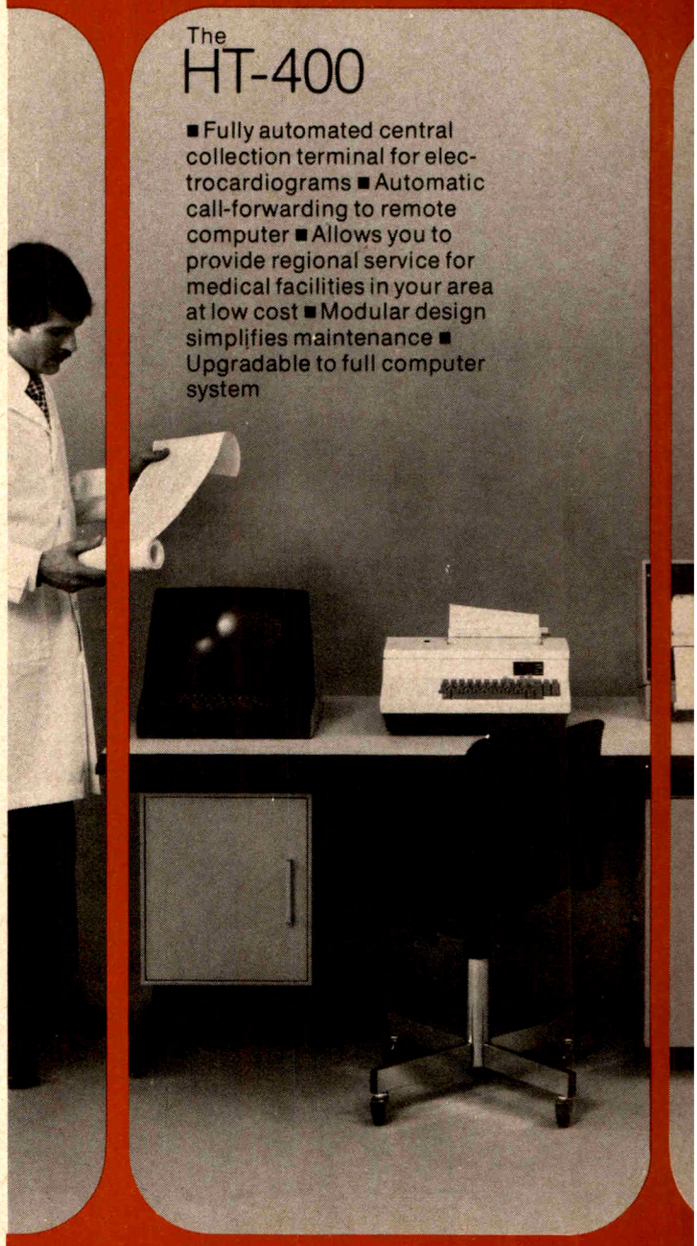
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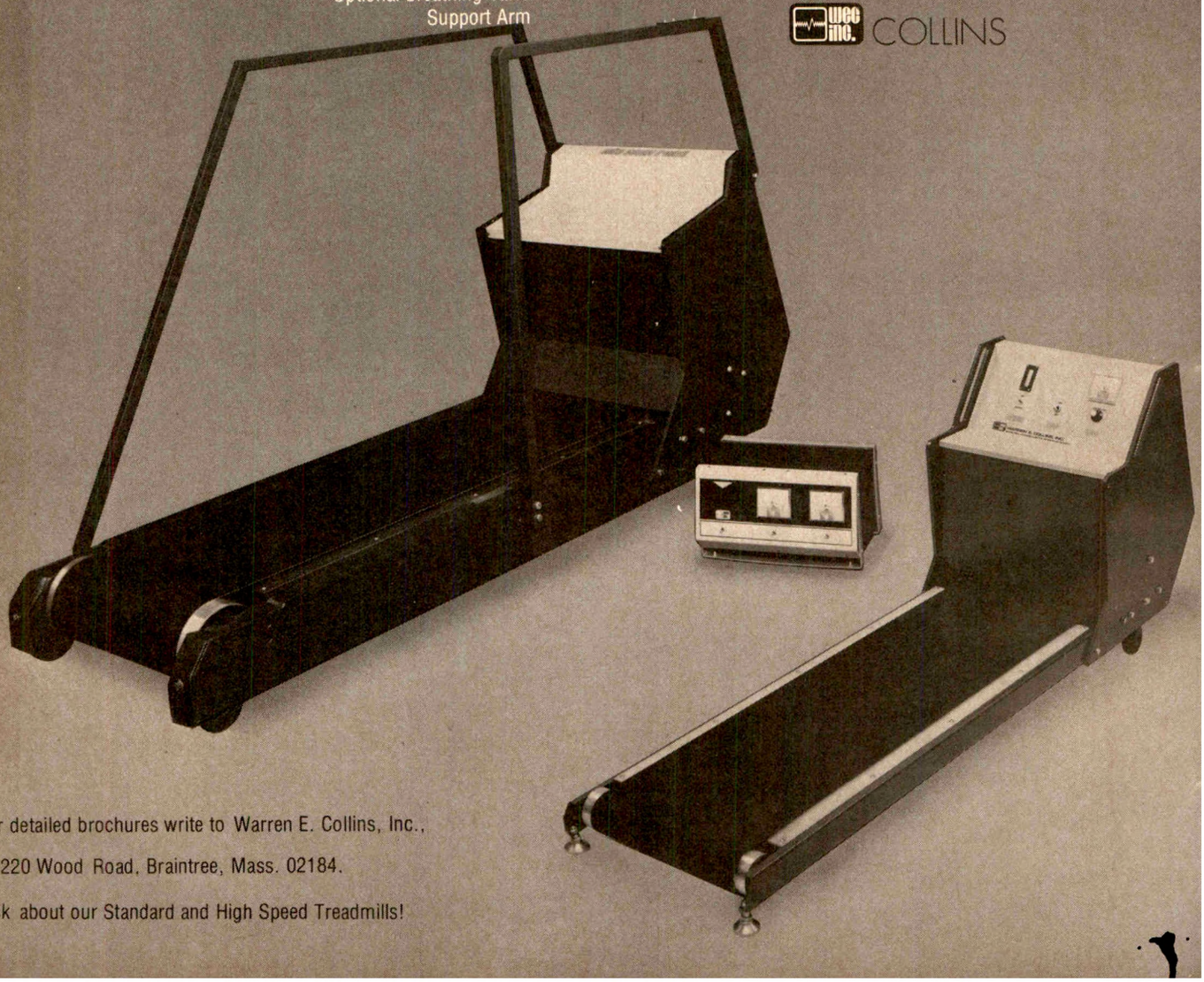
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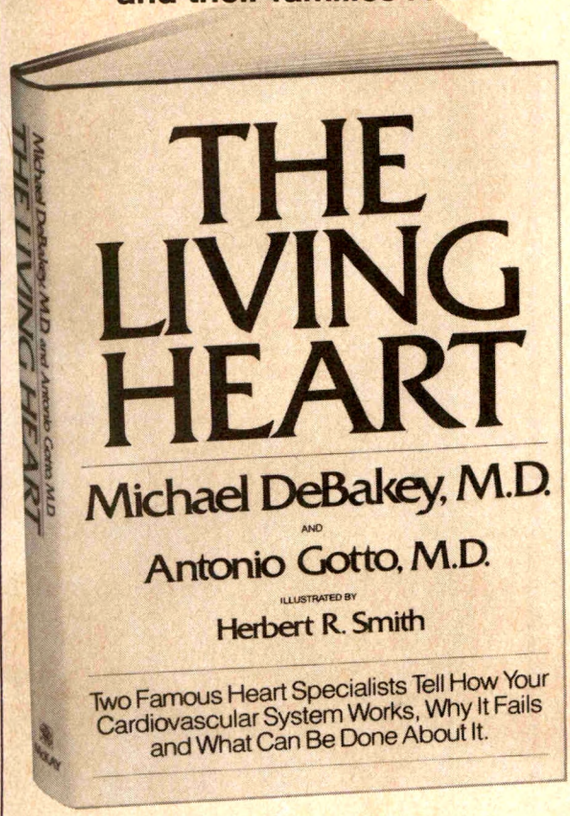
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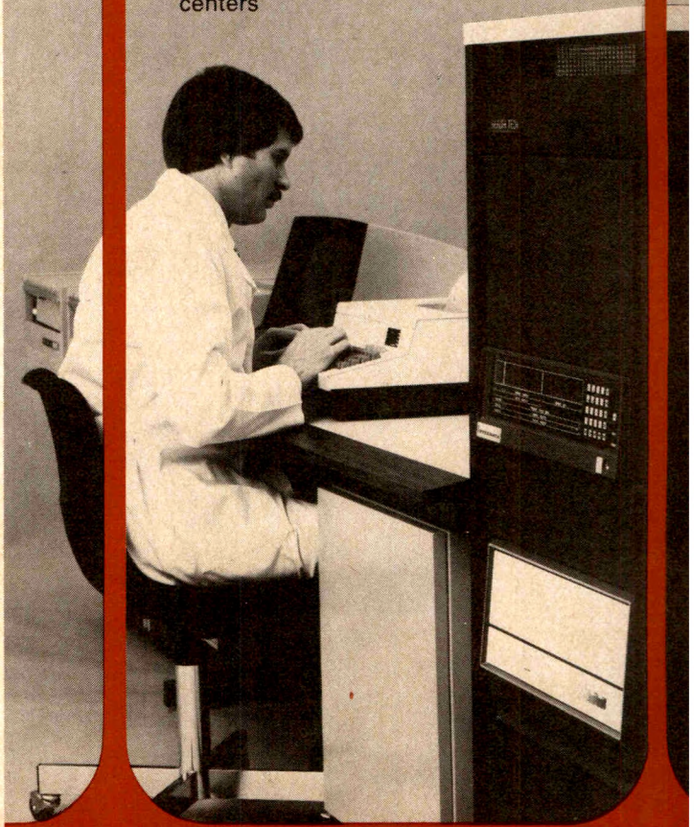
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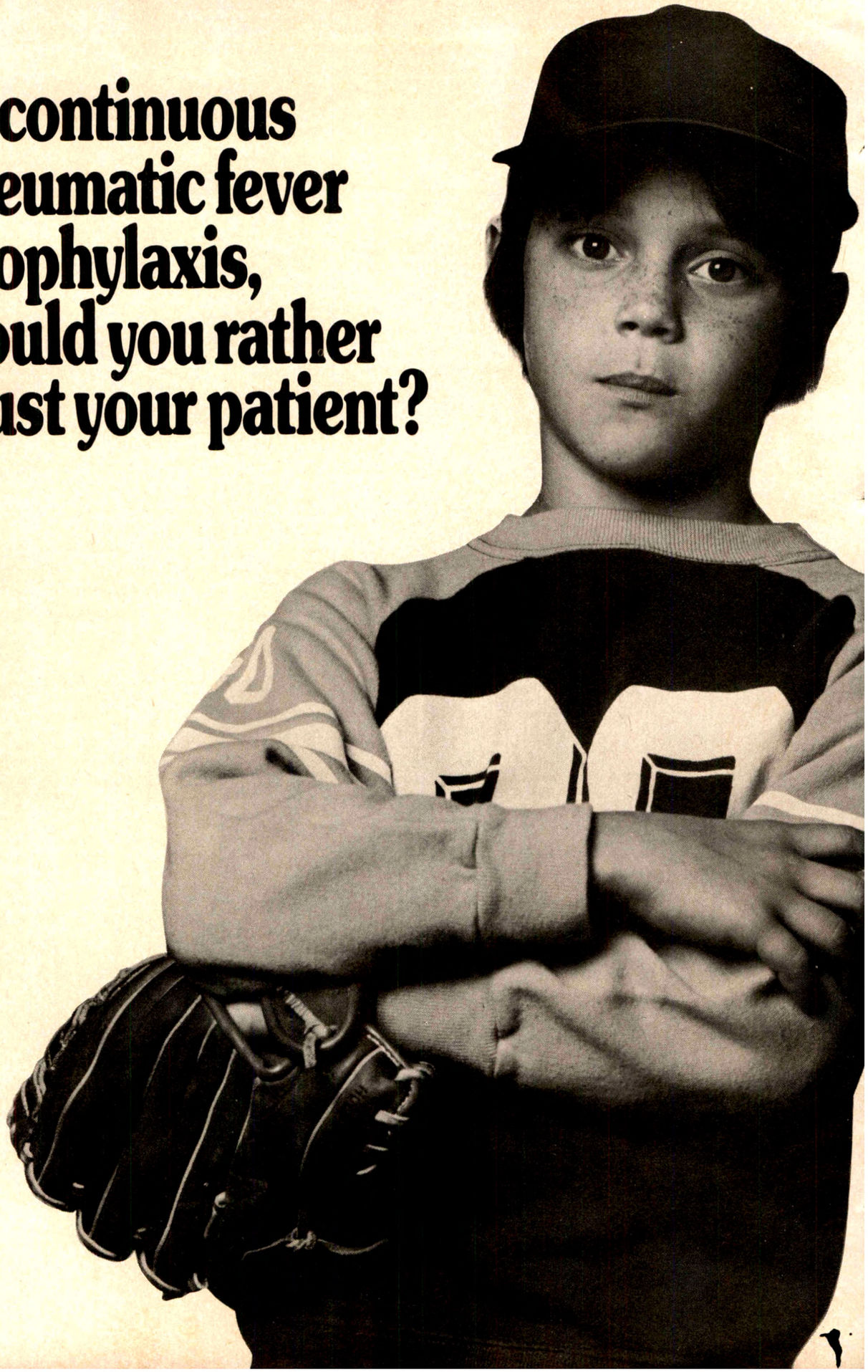


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In continuous rheumatic fever prophylaxis, would you rather trust your patient?



Or yourself?

Injection penicillin G benzathine is recommended as the method of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever. One reason is that just one injection of 1,200,000 units, once a month, usually offers effective and continuous prophylaxis. So there's no need to worry that your patient will forget to take a tablet every day.

Mild to moderate group A streptococcal pharyngitis (without bacteremia) therapy is in your hands, too. Because a single injection (600,000 to 900,000 units in children and 1,200,000 units in adults) usually maintains serum concentrations for the ten days deemed necessary to eradicate the streptococci and preclude the initial onset of rheumatic fever.†

You, more than anyone else, know the importance of effective and continued rheumatic fever prophylaxis. So is there any question of whom you'd rather trust?

*Rheumatic Fever Committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.
Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections —Syphilis, yaws, bejel, and pinta

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea —Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

†In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units penicillin G benzathine as active ingredient in aqueous suspension): 300,000 units per ml.—10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben and 0.14 mg. propylparaben.

600,000 units in 1-ml. TUBEX* (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-ml. fill in 2-ml. TUBEX, packages of 10.

1,200,000 units in 2-ml. TUBEX, packages of 10, and in 2-ml. single-dose disposable syringe, package of 10.

2,400,000 units in 4-ml. single-dose disposable syringe, packages of 10

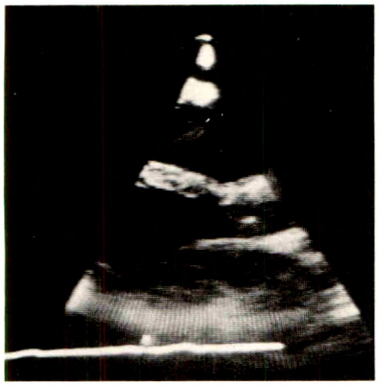
Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.

INJECTION
Bicillin® L-A
(sterile penicillin G benzathine suspension)

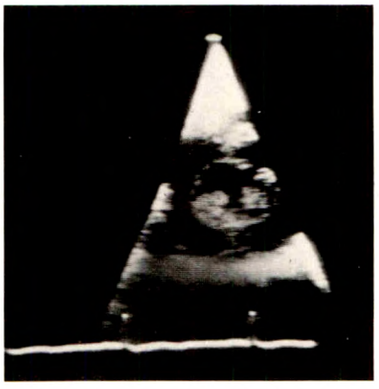
Once-a-month rheumatic fever prophylaxis.

Wyeth Laboratories
Philadelphia, Pa. 19101

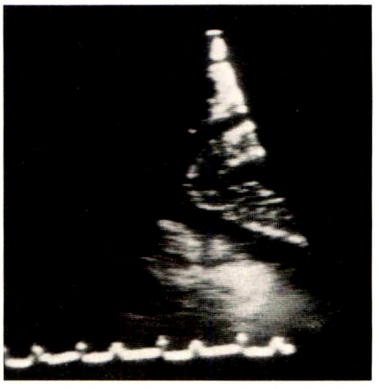
The dollars and sense of real time.



Large angle longitudinal view, showing MV, AV, IVS, LA, LV and RV.



Transverse view of Left Ventricle, Papillary Muscle.



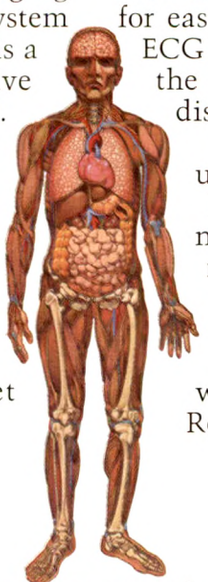
Apex of Left Ventricle, Pericardial Effusion.

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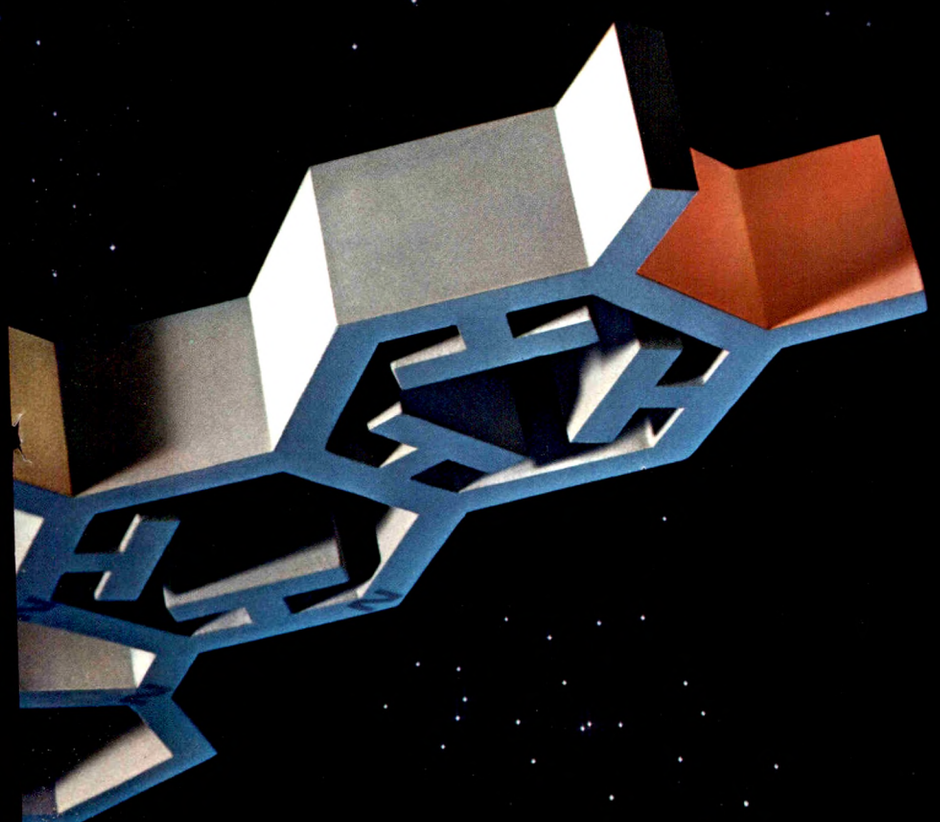
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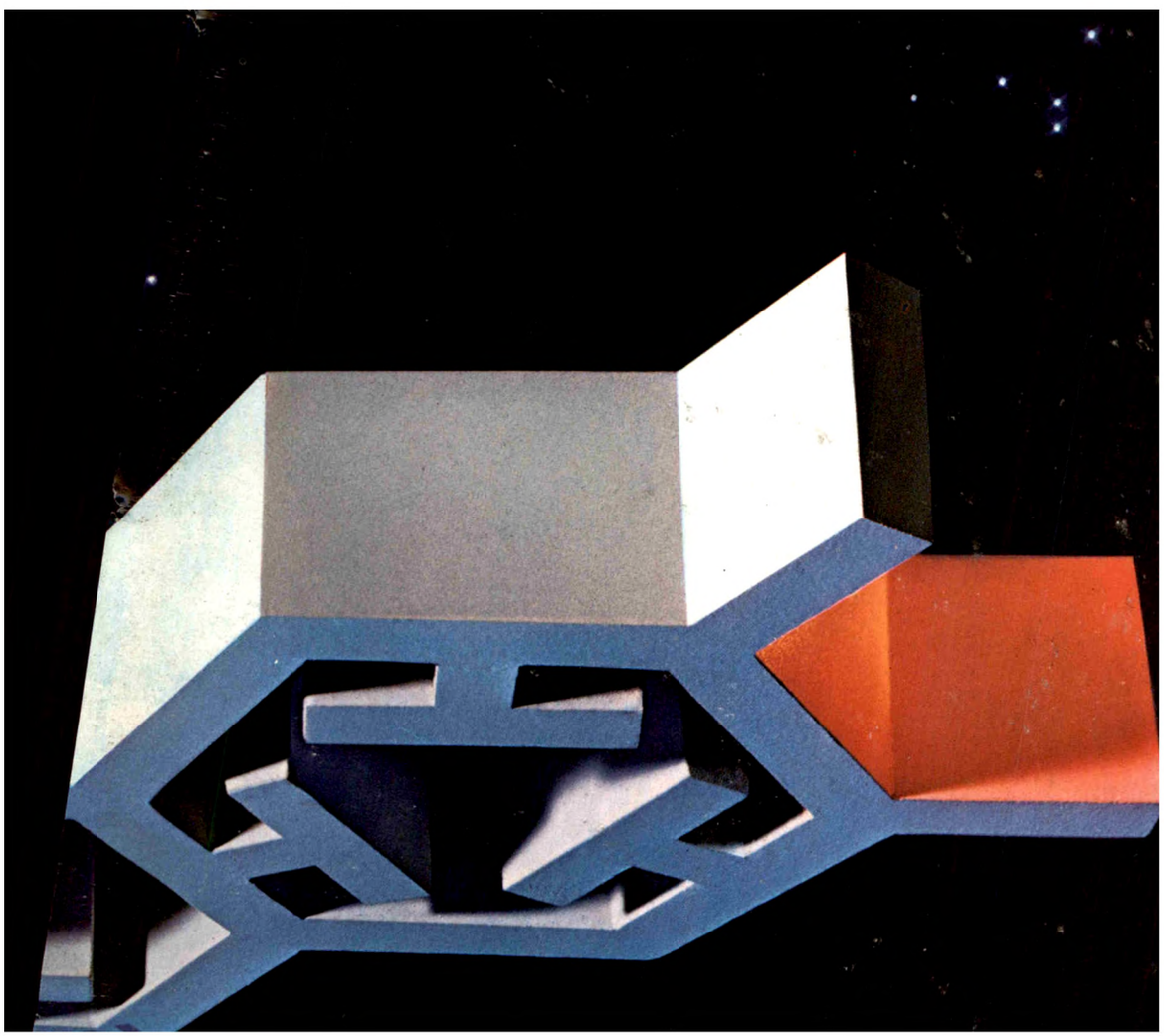
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- chemically and pharmacologically unique vasodilator
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- no tolerance observed in long-term therapy*



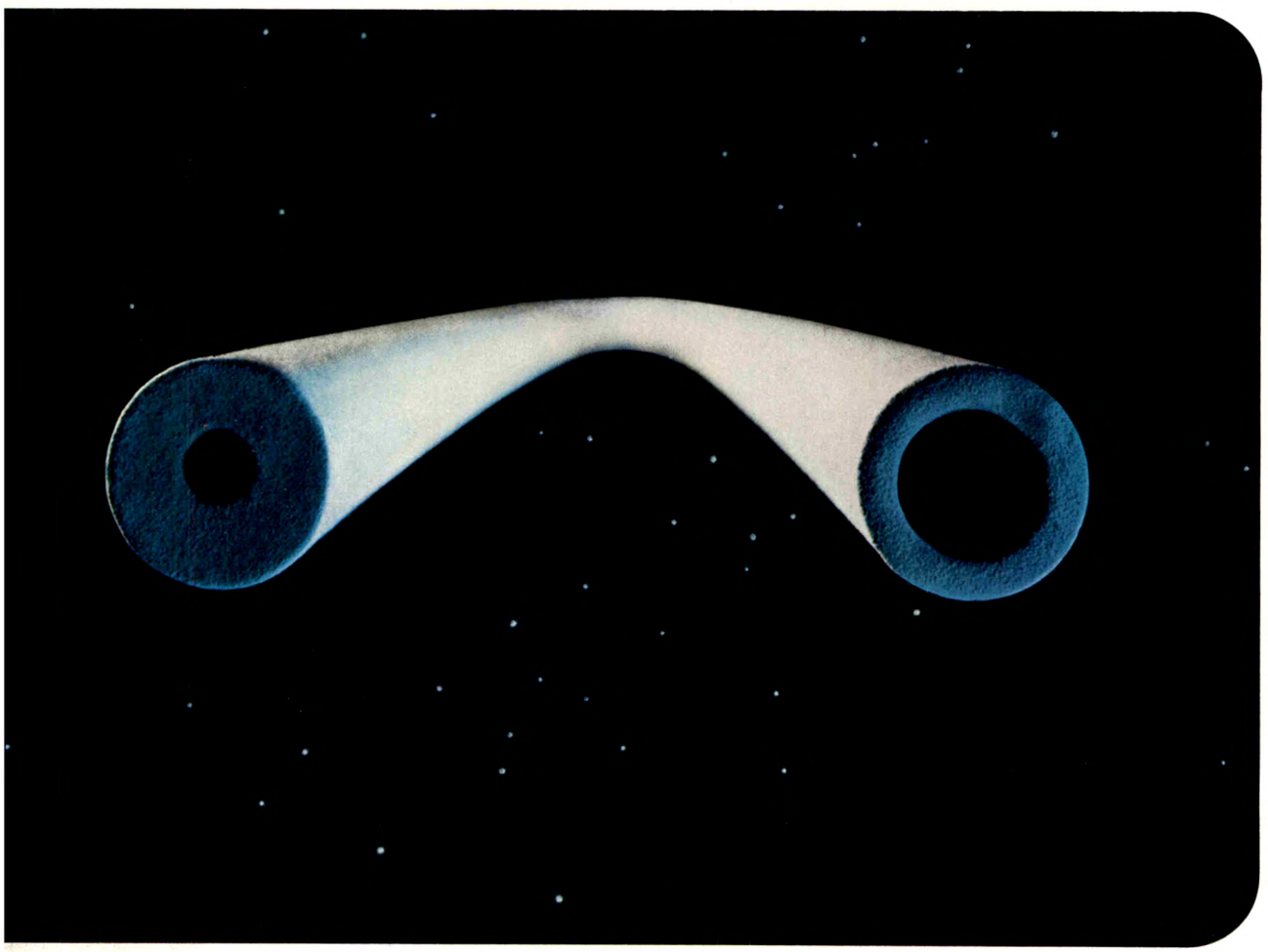
The above is an artistic rendition of the molecular structure of prazosin.

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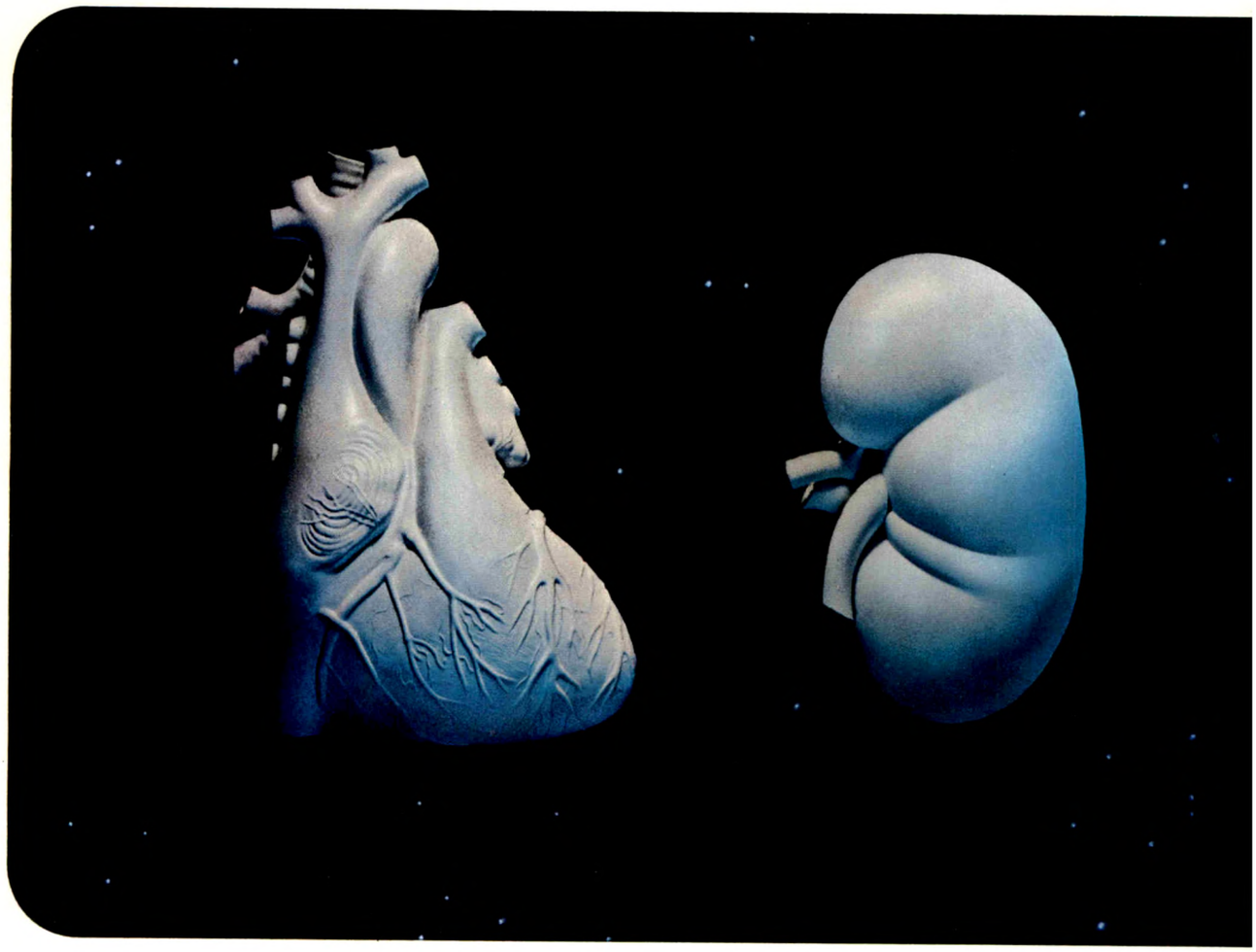
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Well suited for long-term therapy because of direct action on the arterioles



- Antihypertensive effects are a direct result of relaxation of arteriolar smooth muscle, with an associated decrease in peripheral resistance without dilatation of venules or consequent venous pooling.

without clinically significant changes in cardiac or renal hemodynamics.



- No significant change in cardiac output. Reflex tachycardia frequently associated with other vasodilators is much less common with Minipress.
- No significant change in renal blood flow or glomerular filtration rate.
- No increase in plasma renin activity.

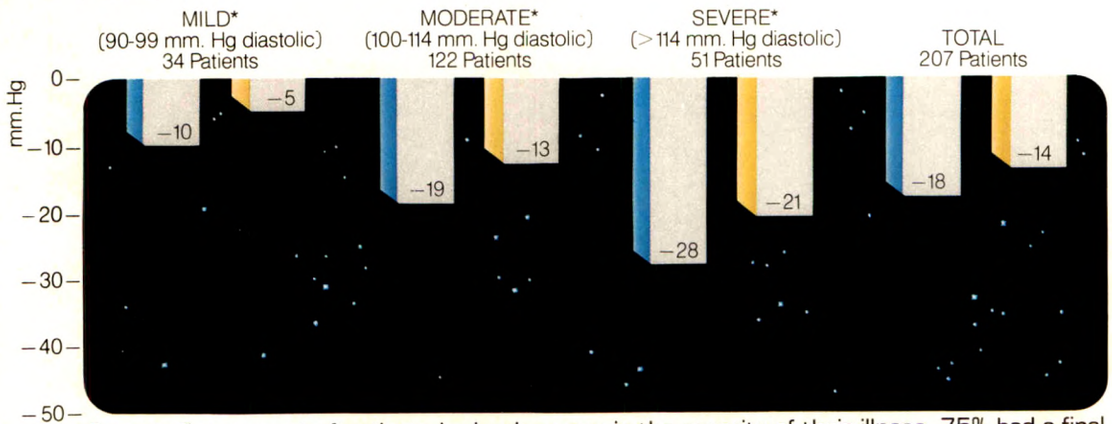
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ANTIHYPERTENSIVE RESPONSE IN ALL PATIENTS (RESPONDING AND NONRESPONDING):
Mean reduction of blood pressure (standing)

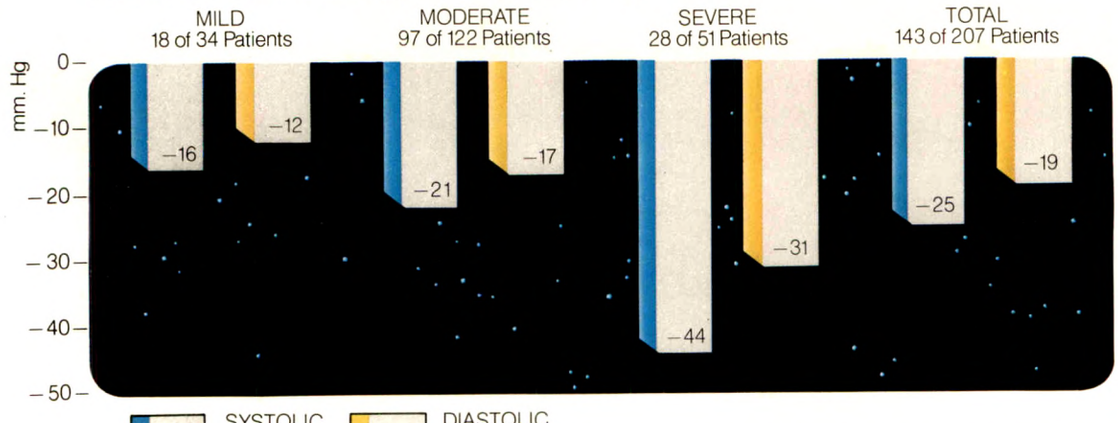
207 patients were treated for 8 weeks or longer and were titrated through the full dosage range (up to 20 mg./day) unless satisfactory response (diastolic below 100 mm. Hg) was achieved at a lower dose level. More than three-fourths of the patients had hypertension of moderate severity or greater.



Seventy-five percent of patients had a decrease in the severity of their illness, 75% had a final standing diastolic below 100 mm. Hg and nearly one-third of the patients had a final standing diastolic below 90 mm. Hg.

*BASELINE SEVERITY

ANTIHYPERTENSIVE EFFECT IN RESPONDING PATIENTS:
Mean reduction of blood pressure (standing)



The pattern of response shown above provides another perspective on the activity of Minipress by illustrating mean blood pressure reductions in those patients who responded to Minipress therapy. For those patients who had moderate to severe hypertension, response was defined as a fall in diastolic blood pressure to less than 100 mm. Hg. For those patients who had mild hypertension, response was defined as a fall in blood pressure to less than 90 mm. Hg.

Well tolerated for long-term antihypertensive therapy.

- The most common reactions associated with Minipress therapy are:

  dizziness (10.3%)
  headache (7.8%)
  drowsiness (7.6%)
  lack of energy (6.9%)
  weakness (6.5%)
  palpitations (5.3%)
  nausea (4.9%)

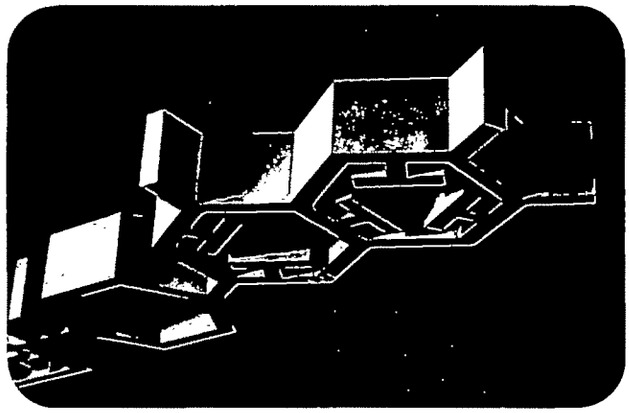
- A small percentage of patients experienced orthostatic hypotension (3.4%) and syncope (1.3%). Patients should always be started on 1-mg. capsules of Minipress. The 2-mg. and 5-mg. capsules are not indicated for initial therapy. (For more detailed descriptions of orthostatic hypotension and syncope, refer to Warnings section in Brief Summary.)

- Minipress was found to be associated with a relatively low incidence of the following side effects often encountered with one or more other antihypertensive agents:

  dry mouth (4.2%)
  nasal congestion (3.7%)
  depression (2.3%)
  diarrhea (1.5%)
  impotence (0.6%)
  tachycardia (0.2%)

  Laboratory abnormalities such as positive Coombs' tests and alterations in serum electrolytes have not been a problem with Minipress therapy.

Please see Brief Summary on last page for indications, warnings and adverse reactions.

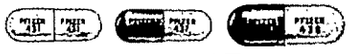


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- Chemically and pharmacologically unique vasodilator.
- Mild to moderate in activity.
- Effective in all grades of hypertension, either alone or in combination with a diuretic and/or other antihypertensive agent.
- Direct action on the arterioles without clinically significant effects on cardiac output, renal blood flow or glomerular filtration rate. Reflex tachycardia frequently associated with other vasodilators is much less common with Minipress.
- No tolerance observed in patients on continuous therapy for periods of up to 5 years.
- Studies in patients on continuous therapy for periods of up to 5 years indicate that Minipress is well suited for long-term therapy.

- Starting dosage: 1 mg t.i.d. (See Dosage and Administration section.)
- Usual maximum recommended dosage: 20 mg daily, given in divided doses.
- Some patients can be maintained adequately on a b.i.d. dosage regimen.
- Available in



1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) Capsules *For Oral Use*

INDICATIONS. MINIPRESS (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS. MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS. The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION. The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. Higher doses usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED. MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437), and 5 mg (blue and white #438) capsules in bottles of 250, and unit dose packages of 100 (10 x 10's).

More detailed information available on request.

Pfizer **LABORATORIES DIVISION**
PFIZER INC.

New Endomyocardial Biopsy Catheter for the Left Ventricle

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A new biopsy catheter specifically made for left ventricular endomyocardial biopsy is described. The biopsy catheter is equipped with a device enabling one to bend the tip at will by rotating a knob on the operating handle. The rate of success in obtaining left ventricular biopsy specimens was very high (100 percent) and there were no serious complications in a group of 10 dogs and in five patients with cardiomyopathy.

Biopsy of the myocardium and endocardium provides definitive information in the study of cardiomyopathy. Among various instruments used in biopsy of the human heart,[1–6] the Konno-Sakakibara biopsy catheter or "bioptome"[7] has proved practical and safe,[6,8] at least for right ventricular biopsy. However, because of its stiffness, the bioptome is sometimes difficult to pass through the aortic valve into the left ventricle using the retrograde approach. A painstaking maneuver to change direction of the bioptome tip or bending the tip in different ways is usually necessary for entry into the left ventricle.[9] This communication describes a new biopsy catheter with a flexible tip specifically made for left ventricular endomyocardial biopsy.

Instrument

The new biopsy catheter consists of two parts:* an ordinary intracardiac catheter with an operating handle at one end and cutting pincers at the exploring end closely resembling the Konno-Sakakibara's bioptome (Fig. 1). By rotating a knob on the operating handle, one can bend the tip of the biopsy catheter about 40° (Fig. 1, inset) so that it can make a U turn that is otherwise only possible with a small catheter. This bending is possible in one plane. The intracardiac catheter measures 120 cm in length and is available in both a small (3.2 mm [tip 3.0 mm]) and a large (3.5 mm [tip 3.3 mm]) diameter. The sliding assembly can be pushed down the long axis of the catheter to open the cutting pincers. By pulling up the sliding assembly one can approximate the pincers. A straight stainless steel stylet of 0.5 mm diameter is inserted through a side hole of the operating handle into the core of the shaft, which is made of coiled stainless steel wire covered with a Desmopan® sleeve. The stylet, pulled out approximately 10 cm while the catheter tip is being bent, is then advanced to the extreme end of the catheter to obtain appropriate stiffness for excision of the cardiac tissue by the pincers. To avoid entrapment of even a small amount of blood inside the catheter, the internal space of the catheter is filled with heparin solution through an inlet that is then closed with a one-way stopcock.

Materials and Procedure

With this instrument the left ventricle was successfully entered in retrograde fashion through the femoral artery in 10 mongrel dogs weighing 15 to 20 kg. In five patients with cardiomyopathy the biopsy catheter was inserted through the femoral artery by arteriotomy and advanced to the left ventricle under fluoroscopic control. The patients were generally heparinized. A slight bend of the tip was necessary to permit passage of the catheter through the aortic arch down to the ascending aorta. With another bend or twist of the biopsy catheter the

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* Manufactured at the Tonokura Ika Kogyo Co., Ltd. and Machida Manufacturing Co., Ltd., Tokyo, Japan.

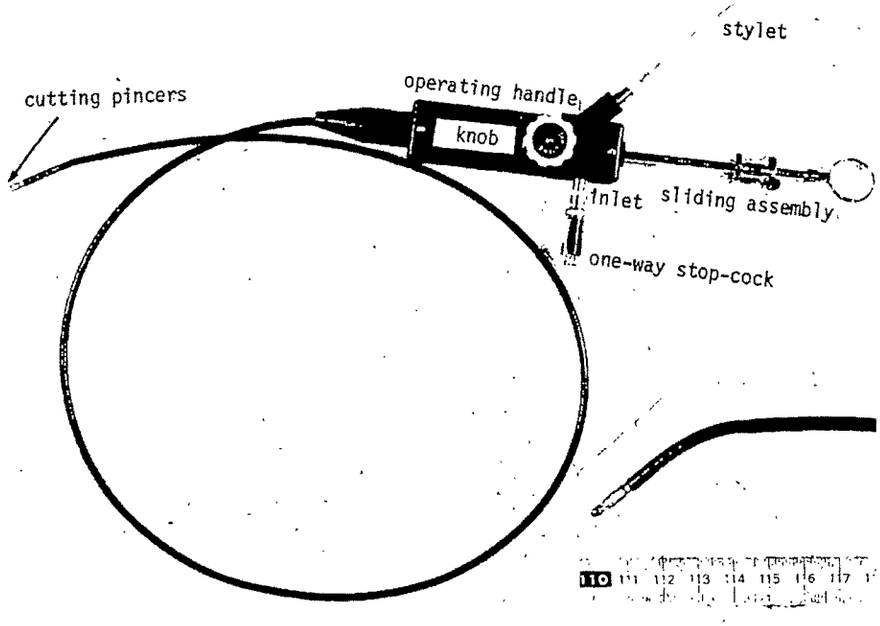


FIGURE 1. New endomyocardial biopsy catheter for the left ventricle. **Inset** (lower right) indicates a bend (about 40°) of the tip of the biopsy catheter.

left ventricle was usually entered easily. When the instrument was introduced into the left ventricle (Fig. 2), the stylet was advanced and the catheter pressed against the apical region of the left ventricular wall. The pincers were opened for excision of the cardiac tissue only after the tip of the instrument was in appropriate contact with the endocardial surface of the left ventricle, as confirmed by the injury pattern of the intracardiac electrocardiogram recorded from the catheter tip.



FIGURE 2. Chest X-ray film with a new endomyocardial biopsy catheter in the left ventricle by way of the femoral artery in a patient with cardiomyopathy.

Results

The rate of success in obtaining biopsy specimens from the left ventricle with this instrument has thus far been 100 percent both in patients and in dogs. Entering the left ventricle was easier in patients than in dogs. The dogs remained active and healthy after left ventricular biopsy. In patients with cardiomyopathy only a few premature ventricular contractions were noted at the time of contact of the tip with the left ventricular endocardium and of excision of the biopsy specimens. There were no serious complications such as endocarditis, mural thrombosis or hemopericardium. The patients have been followed up for 1 to 6 months. The biopsy specimens of the left ventricle were subjected to light (Fig. 3, left) and electron microscopic (Fig. 3, right) examinations and histochemical and immunofluorescent studies.

Discussion

Because the left ventricle is the chamber mainly involved in many adult patients with cardiomyopathy, biopsy specimens from the left ventricle are generally more informative than those from the right in detecting structural changes in cardiomyopathy.[9] The microscopic appearance of left ventricular biopsy specimens differed from that of right ventricular specimens in 60 percent of cases.[10] Percutaneous needle biopsy,[11,12] an obviously hazardous procedure, is still being performed occasionally in the left ventricle because of difficulty in passing the Konno-Sakakibara biopsy catheter through the aortic valve. Recently, Brooksby et al.[10,13] described the St. Thomas long sheath technique for introducing biopsy forceps into the left ventricle. The method seems to be of advantage in positioning the sheath and biopsy catheter in the left ventricle and in enabling multiple specimens to be taken in rapid succession. However, there remains the possibility of introducing air and

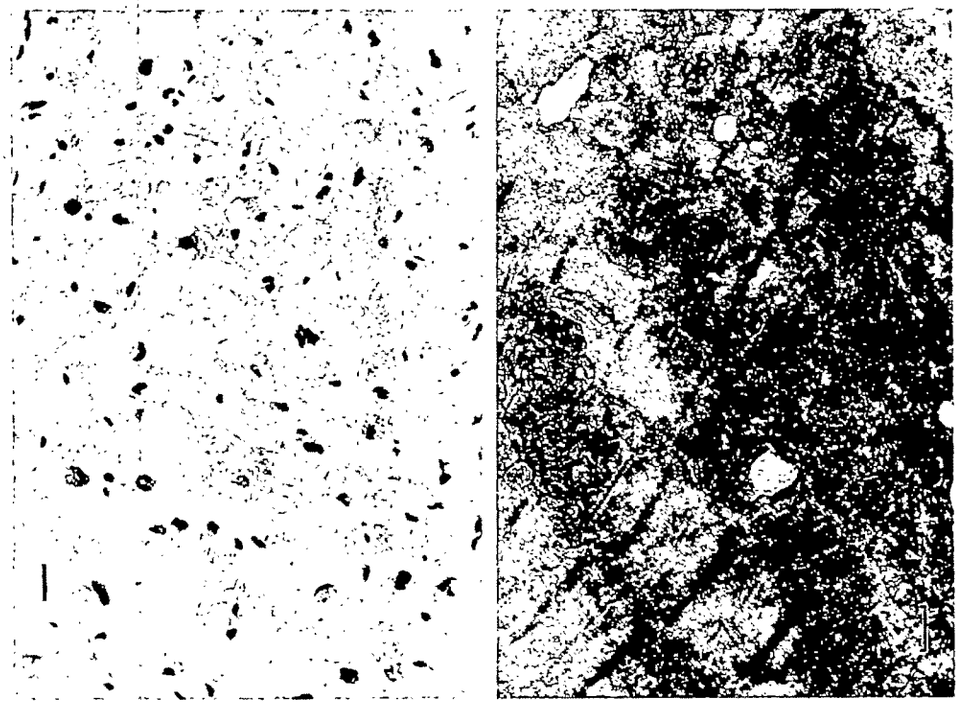


FIGURE 3. Light **(left)** and electron **(right)** photomicrographs of a biopsy specimen obtained from the left ventricle with the new endomyocardial biopsy catheter. Scale: 20 μ **(left)**, 1 μ **(right).** The light micrograph **(left)** shows mild hypertrophy of myocardial cells with large nuclei. The electron micrograph **(right)** shows regularly shaped and normally arranged myofibrils with partially increased mitochondria. (Hematoxylin-eosin ×250 [**left**] and ×6,000 [**right**], reduced by 23 percent.)

blood clot when passing the biopsy catheter down the sheath with the trapped air or blood inside it.

Our instrument eliminates these disadvantages. It was made with the thought that a device for changing direction of the biopsy catheter tip at will might be of help in passing the catheter through the aortic valve. On the other hand, a flexible tip is unfavorable for excising cardiac tissue. Therefore, once the left ventricle is entered, the stylet should be advanced to give adequate stiffness to the flexible tip. Thus the success rate of obtaining biopsy specimens from the left ventricle and the safety of the technique have been much improved. Introduction of the biopsy catheter into the femoral artery requires arteriotomy, which is not disadvantageous but rather is recommended because of its safety in patients whose arteries are small. We believe that left ventricular biopsy will be performed more easily and safely with this new biopsy catheter.

Acknowledgment

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Surgical Correction of Atrioventricular Canal During the First Year of Life

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Eight infants less than 1 year of age with an atrioventricular (A-V) canal defect (five with the complete form and three with the partial form) had definitive surgical correction performed because of intractable congestive heart failure. At operation, the infants weighed 2.9 to 6.5 kg. There was one operative death and one late death. The six surviving children were all doing well when followed up 10 months to more than 4 years postoperatively. This small series demonstrates that complete connection of A-V canal is possible even in very small infants and that chances of success are excellent. The infant with this defect who is not progressing with medical management should undergo definitive surgical correction, and a strong argument can be made for elective complete repair in all patients with this lesion, who have severe pulmonary hypertension, during the first 1 or 2 years of life.

A 1973 publication from the Mayo Clinic[1] reported the successful surgical correction of complete atrioventricular (A-V) canal in two infants less than 1 year old. Since then, additional experience has been gained with repair of both the complete and partial forms of this lesion during the first year of life. Since the initial report, all infants with A-V canal who presented at our institution with intractable congestive heart failure have been managed by an attempt at definitive correction rather than pulmonary arterial banding. All eight children in this series were making unsatisfactory progress while on an optimal medical program and needed surgical intervention in order to survive.

Material and Methods

Patients: Five patients were female and three were male (Table I); none had Down's syndrome. In all instances, the diagnosis was established with cardiac catheterization: Four patients were studied in our cardiac laboratory and four at other institutions. Three patients had the partial form of A-V canal, and five had the complete form. The partial form has been defined[2] as a condition in which the A-V valves are adherent to the crest of the underlying ventricular septum so that no interventricular defect is present. In the complete form, the A-V valve leaflets do not adhere to the ventricular septum and there is an interventricular communication.

One of the three patients with partial A-V canal had an accessory mitral valve orifice. Three of the five patients with the complete form had the typical type A deformity, as defined by Rastelli et al.[3] The anatomic features in the other two were somewhat atypical but most closely resembled those of type A: One patient had an accessory mitral orifice and the other had multiple ventricular septal defects. Three patients had an additional small secundum atrial septal defect. All patients had a very large left to right shunt and severe mitral valve incompetence, with regurgitation of left ventricular blood into the right or the left atrium, or both.

Operative repair: In all instances surgery was performed in a manner previously described.[2,4–6] Five patients (Cases 1, 2, 4, 6 and 7) underwent correction on total cardiopulmonary bypass (perfusate temperature 30° C) with intermittent periods of aortic cross-clamping. The total duration of cardiopulmonary bypass ranged from 60 to 91 minutes, and the total length of aortic cross-

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TABLE I

Data on Eight Patients Who Underwent Atrioventricular Canal Repair Before Age 1 Year

Case no.	Type of A-V Canal	Surgery: Date	Surgery: Patient Age (mo)	Surgery: Patient Weight (kg)	Intraoperative Findings: Anatomy	Pre-Repair Pressures (mm Hg): RV	PA	LV	Ao	LA	Post-Repair Pressures (mm Hg): RV	PA	LV	Ao	LA	Post-Repair Dye Curves	Follow-Up: Interval (mo)	Follow-Up: Patient Status
1	Partial	Mar 1972	11	6.5	Typical	57/6	50/12	90/5	...	20/10	40/10	...	120/10	...	25/10	Minimal MI	53	Excellent
2	Partial	Apr 1972	10	6.4	Accessory mitral orifice, additional secundum ASD	48/5	...	72/0	60/40	20/15	32/7	...	110/5	110/60	22/10	Minimal MI	52	Excellent
3*	Complete	Nov 1972	6	4.8	Type A	50/20	...	60/10	...	24/12	25/10	...	75/0	...	17/5	Moderate MI	45	Excellent
4	Complete	Dec 1973	10	5.1	Type A, 4 small VSDs, additional secundum ASD	55/0	55/20	70/0	...	18/10	40/6	...	100/5	...	22/15	Moderate MI	...	Operative death
5	Complete	Jan 1974	3	3.5	Type A, accessory mitral orifice	74/5	...	82/4	...	28/6	35/5	...	...	85/45	20/16	Not performed	31	Excellent
6	Partial	Apr 1975	8	4.7	Typical	52/10	...	67/8	...	28/12	45/10	...	80/15	...	28/15	Minimal MI	...	Late death, 4.5 mo postop
7	Complete	May 1975	9	5.3	Type A	65/0	...	65/0	...	15/5	55/0	...	110/0	...	16/6	Minimal MI	15	Excellent
8	Complete	Oct 1975	1.5	2.9	Type A, additional secundum ASD	55/0	...	55/0	...	10/4	40/5	...	85/5	...	25/10	Not performed	10	Excellent

* Previously reported on.[1]

Ao = aortic; ASD = atrial septal defect; A-V = atrioventricular; LA = left atrial; LV = left ventricular; MI = mitral insufficiency; PA = pulmonary arterial; postop = postoperative; RV = right ventricular; VSD = ventricular septal defect.

clamping time ranged from 12 to 49 minutes; the maximal single period of cross-clamping time was 22 minutes. The three youngest patients (Cases 3, 5 and 8) were placed on extracorporeal circulation and their body temperatures lowered to 16° to 18° C. In these three, repair was performed during total circulatory arrest, which lasted from 42 to 50 minutes. Intraoperative pressure recordings were obtained in all patients initially before the institution of cardiopulmonary bypass and again after completion of the repair with the patient no longer on extracorporeal circulation (Table I).

Intraoperative and post-repair double sampling dye-dilution curves, with indocyanine green injected into the left ventricle and simultaneous sampling in the left atrium and aorta, were performed in six patients to assess the degree of residual mitral valve incompetence (Table I). In the patients with minimal residual mitral insufficiency, the regurgitant fraction, as observed from the dye curves, was 10 percent or less, whereas in the two patients with moderate mitral incompetence, the regurgitant fraction was approximately 30 percent.

Results

Operative mortality: There was one operative death (Case 4). This child had deficiency of mitral leaflet tissue noted at operation and, after repair, the intraoperative dye curves showed evidence of moderate residual mitral valve incompetence. The cardiac output was good immediately after operation but began to deteriorate approximately 6 hours later and, despite supportive measures, the child died 12 hours after operation. Permission to perform an autopsy was refused.

Late mortality: There was one late death (Case 6). Despite apparently good operative repair with minimal residual mitral insufficiency, this child did not do well after returning home, continuing to have congestive heart failure and recurrent pulmonary infections. Five weeks after operation, she reportedly underwent a right middle lobectomy for previously recognized congenital lobar emphysema of this lobe. Her condition did not improve and, 2 months after cardiac repair, repeat cardiac catheterization was performed at our institution. This study revealed no residual intracardiac shunt, and simultaneous wedge pressure and left ventricular pressure recordings showed no evidence of mitral stenosis. A left ventriculogram revealed only minimal residual mitral incompetence, but the left ventricular end-diastolic pressure was elevated to 25 mm Hg, and angiocardiography revealed that the left ventricular cavity was unusually small and that the ventricle contracted poorly. This patient therefore appeared to have the form of A-V canal classified by Bharati and Lev[7] as a dominant right defect with a small left ventricle. This child's condition gradually deteriorated, and she died in her home community 4 1/2 months after cardiac operation. Because autopsy was not performed the cause of the left ventricular failure, the presumed cause of death, was not conclusively determined.

Follow-up: Six of the patients have survived, and recent follow-up information was obtained 10 months to more than 4 years after operation either by reexamination at the Mayo Clinic or by communication with the child's physician in the home community. All six are presently doing well and have no significant symptoms. None exhibit signs of congestive heart failure, and all have shown a marked acceleration of growth as well as a significant reduction in relative heart size. One child has no audible cardiac murmur, four have a grade 2/6 apical systolic murmur and one has a grade 3/6 apical systolic murmur. No patient has a diastolic murmur. Only one of the six survivors (Case 5) has undergone postoperative cardiac catheterization, and this study, electively performed in our laboratory 2 1/2 years after operation, showed mild mitral incompetence with a very small residual left to right shunt at the atrial level. The mean pulmonary arterial wedge pressure was 14 mm Hg; the pulmonary arterial pressure was 34/16 mm Hg.

Discussion

A-V canal is a complex congenital cardiac anomaly that frequently results in congestive heart failure during infancy. Four of our eight patients had signs of heart failure during the first month of life, and all had such signs by age 3 months. Some of these infants may respond to medical therapy, but a significant number will not, and these most often have significant mitral valve insufficiency in addition to a large left to right shunt. Although pulmonary arterial banding may provide effective surgical palliation for the infant with congestive heart failure primarily due to a large intracardiac shunt, it is often not effective in alleviating heart failure in the patients with additional severe A-V valve incompetence.[8,9] Rudolph[10] has postulated the hemodynamic basis by which one might anticipate such failure of pulmonary arterial banding to improve the condition of patients with A-V canal and severe mitral valve incompetence.

Indications for early surgical correction: Because no effective surgical palliation is available for the child with A-V canal with refractory heart failure caused primarily by mitral incompetence, definitive surgical correction offers the only chance for survival. Good operative results have been achieved for nearly a decade in older patients with this lesion.[2,5,11] However, at the time of our 1973 report,[1] only six attempts at complete repair in children less than 2 years old had been reported in the English language literature; only two children had survived and the condition of one was only "marginally improved."

Since the 1973 report, the evolution of the surgical management of A-V canal in infancy has been parallel to that seen earlier in simple ventricular septal defect. Although our series is small, our experience has demonstrated that this lesion can be accurately repaired, even in the very small infant, and that such correction can be accomplished at an acceptable risk. We believe that all infants with this lesion who have intractable heart failure should undergo definitive correction although the anatomic characteristics of the A-V valves often make it impossible to eliminate mitral incompetence. Residual mitral incompetence, if mild, seems to be immediately well tolerated and did not prevent our surgical survivors from experiencing complete compensation with a resultant acceleration of growth and alleviation of symptoms. Even if longer follow-up should establish that eventual reoperation for mitral valve replacement is necessary for some survivors, this would not be an argument against early correction when one considers the alternatives.

Elective closure of simple ventricular septal defect large enough to transmit systemic level pressure to the pulmonary circuit is now recommended in children who are less than 2 years old[12] because irreversible pulmo-

nary arteriolar changes tend to develop in such patients if the defect remains open beyond this age. Such defects are now electively closed during the first 2 years of life at an operative risk not significantly different from that achieved in older patients.[13] Observations of the natural history of A-V canal over many years have established that pulmonary vascular disease is likely to develop early in patients with this lesion, particularly those with its complete form. A recent pathologic study[14] reemphasized the need for early surgical intervention in complete A-V canal: Eight of 12 patients with this lesion aged 1 year or older who had not had pulmonary banding were found to have Heath-Edwards[15] pulmonary arteriolar lesions of grade III or greater. Of the 24 patients in that study who underwent pulmonary arterial banding, 12 patients died (50 percent)—a mortality experience not unlike that reported by other centers.[8,9] Because of the conclusive evidence that patients who have this lesion are at a high risk of having severe pulmonary vascular obstructive disease early and because of the documented high mortality rate and frequent ineffectiveness of pulmonary arterial banding, there is a compelling argument for early elective definitive correction of this lesion. This would be highly desirable before the child becomes 2 years old and probably should be accomplished during the first year of life. The results obtained in our small series of patients, all of whom had severe congestive heart failure before operation, indicate that such a plan is feasible and that the surgical approach for A-V canal will eventually coincide with that now used in simple ventricular septal defect.

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Congenital Pulmonary Atresia With Tricuspid Insufficiency: Morphologic Study

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In an anatomic study of 21 cases of pulmonary atresia with tricuspid insufficiency (pulmonary atresia with intact ventricular septum, type II), the morphologic features of the tricuspid valve and the right ventricle were found to differ greatly from those seen in pulmonary atresia with tricuspid stenosis (pulmonary atresia with intact ventricular septum, type I). Morphologically, pulmonary atresia with tricuspid insufficiency (type II) has a greater resemblance to Ebstein's disease with pulmonary atresia than to type I pulmonary atresia. The anomaly may be more amenable to surgery than pulmonary atresia with tricuspid stenosis because the right ventricle in the former may be converted into a functional chamber by a valvotomy combined with a shunting procedure and atrial septostomy.

Pulmonary atresia with intact ventricular septum is usually classified into two types: type I, with small right ventricle (pulmonary atresia with tricuspid stenosis) and type II, with large right ventricle (pulmonary atresia with tricuspid insufficiency).[1–36] Considerable attention has been paid to type I clinically and pathologically, but insufficient attention has been given to the anatomic features of the relatively rare type II. Because this type may be more amenable to surgery,[35] we undertook an anatomic study of this type.

Material and Methods

Patients: The anatomic features in 21 cases of pulmonary atresia with tricuspid insufficiency were studied. The patients ranged in age from stillborn to 18 months; 11 were male and 10 female. Fifteen (71.4 percent) were less than 48 hours old, and four (19 percent) were 3 to 6 days old. One (4.8 percent) survived to 18 days, and one (4.8 percent) to 18 months. The oldest survivor had a milder form of the anomaly. One patient died immediately after a Glenn procedure, three immediately after a pulmonary valvotomy and one while the pericardium was being opened.

Fifteen cases came from the Congenital Heart Disease Research and Training Center and six cases from the Armed Forces Institute of Pathology. The former were found among 4,250 cases of congenital heart disease studied at the Center. Excluded from this study were cases of Ebstein's disease with pulmonary atresia, isolated enlargement of the right atrium, absence of the tricuspid valve or isolated tricuspid insufficiency.

Anatomy: The size of the chambers and orifices and the thickness of the walls of the chambers in these cases were compared with those of normal hearts as previously described.[37,38] A block was taken from the inferior leaflet of the tricuspid valve of 1 of the 21 patients, 35 hours old, and from the inferior leaflet of the tricuspid valve of two patients, 1 day and 3 days old, respectively, with pulmonary atresia with tricuspid stenosis. These were serially sectioned and every fifth section was retained. The sections were consecutively stained with hematoxylin-eosin, Weigert-van Gieson, alcian blue and periodic-acid Schiff stains. These sections were compared with those of a similarly stained tricuspid valve of a normal heart of a 35 hour old child.

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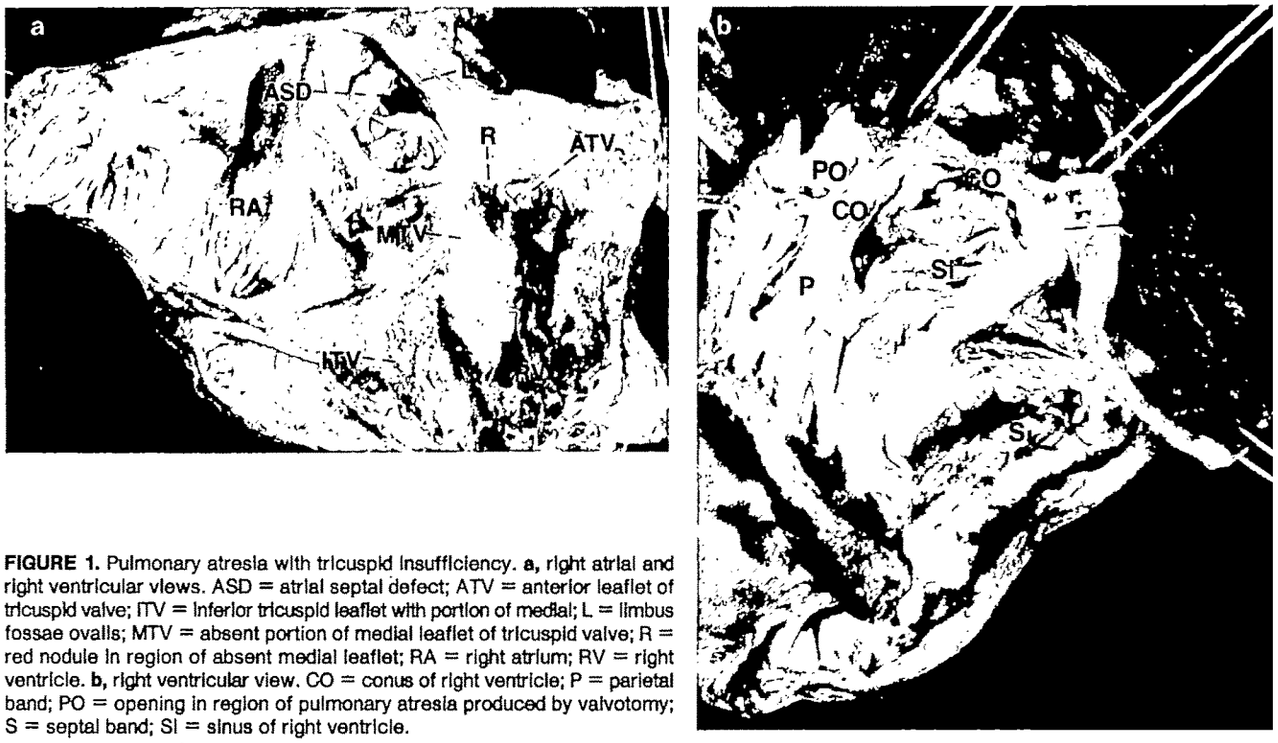


FIGURE 1. Pulmonary atresia with tricuspid insufficiency. **a,** right atrial and right ventricular views. ASD = atrial septal defect; ATV = anterior leaflet of tricuspid valve; ITV = inferior tricuspid leaflet with portion of medial; L = limbus fossae ovalis; MTV = absent portion of medial leaflet of tricuspid valve; R = red nodule in region of absent medial leaflet; RA = right atrium; RV = right ventricle. **b,** right ventricular view. CO = conus of right ventricle; P = parietal band; PO = opening in region of pulmonary atresia produced by valvotomy; S = septal band; SI = sinus of right ventricle.

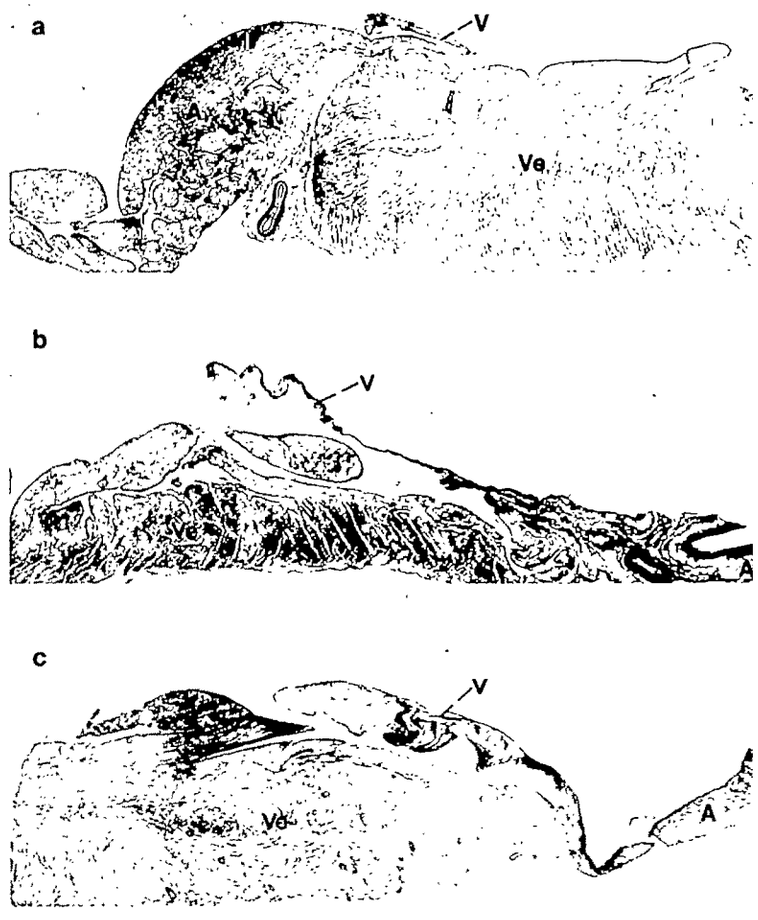


FIGURE 2. Tricuspid valves. **a,** of a 35 hour old normal child; **b,** of a 35 hour old child with pulmonary atresia with tricuspid insufficiency; **c,** of a 1 day old child with pulmonary atresia with tricuspid stenosis. A = atrium; V = valve; Ve = ventricle. (Weigart-van Gieson X11.5, reduced by 35 percent.)

Anatomic Findings

The tricuspid orifice and valve of pulmonary atresia with tricuspid insufficiency (Fig. 1): *Gross examination:* The tricuspid orifice was enlarged in 18 and of normal size in 3 cases. The tricuspid valve was markedly abnormal in all. The anterior leaflet was usually greatly enlarged (Fig. 1a), often obstructing the outflow tract. The valve in some areas was thickened and in some areas was thinned with small nodular formations in the line of closure, edge and body. Its connections were abnormal, from the standpoint of the number or size of the anterior papillary muscle or muscles or the mode of attachment or architecture of these papillary muscles (Fig. 1a). The anterior leaflet was often attached to the parietal band. In a few hearts the anterior leaflet was perforated. The medial leaflet was either absent wholly or in part or was considerably enlarged. In all cases, when present, the medial leaflet was thickened in some areas and thinned in others, and it was irregularly tethered to the wall either directly or by small chordae tendineae and had no chordae attached to the edge. When present, the leaflet often contained small multiple nodular formations. When absent, in a few cases bits of valve tissue were present more distally in the right ventricle. In several cases little red projections were attached to this leaflet or to the wall where the leaflet should be (Fig. 1a). The inferior leaflet was likewise enlarged and partly tethered. Its substance was thickened in some areas and thinned in others. It was sometimes attached to small papillary muscles. In several cases the medial and inferior leaflets were combined into one leaflet. Where valve tissue was present, in all leaflets, it originated at the anulus with the exception of a few bits of valve tissue present more distally in the medial leaflet region.

Microscopic examination: Compared with a valve of a normal child of this age (Fig. 2a and 3a), the tricuspid valve of pulmonary atresia with tricuspid insufficiency showed certain differences. The valve in the latter was much longer and thinner than in the normal child (Fig. 2, a and b). Many thin areas had only fibrosa and no spongiosa (Fig. 3b). However, some localized areas of thickening consisted mostly of spongiosa (Fig. 3c); these were present in the middle of the valve but especially in the periphery. Although the proximal part of the valve was well elastified, the distal part was hypoelastified. The valve contained the same kind of cells as the normal valve, but in spots there were small papilliferous formations of cells on the periphery not seen in the normal. The proximalis and distalis did not show remarkable changes from the normal. Both the fibrosa and spongiosa contained the same amount of mucopolysaccharides as the normal, and the anulus and fibrosa showed the usual periodic acid-Schiff positive material for this age compared with the findings in the normal valve. The valve in pulmonary atresia with tricuspid stenosis was of similar length but thicker than normal (Fig. 2c). This was due to the thickness of the basal fibrosa (Fig. 3d) and in one case a copious amount of spongiosa (Fig. 3e) in the periphery. The proximalis was well elastified, but the peripheral portion of the valve showed hypoelastification. Vacuolization of the spongiosa was evident (Fig. 3e). The mucopolysaccharides and periodic acid-Schiff–staining material were normal for the amount of fibrosa and spongiosa.

The pulmonary valve in pulmonary atresia with tricuspid insufficiency: Although the orifice was atretic, there was agglutination of three incomplete cusps. The type of cusp was identical to that seen in pulmonary valve stenosis with normal aortic root—that is, partial cusps forming a diaphragm with three raphés radiating from it.

The cardiac chambers in pulmonary atresia with tricuspid insufficiency: *The right atrium* was tremendously enlarged (Fig. 1a), especially the appendage, much more so than in pulmonary atresia with tricuspid stenosis. In most cases its wall was thickened, but in a few cases it was thinner than normal. In some cases the eustachian valve was greatly enlarged, and in some a pseudo-septum was formed by this valve. A spatio-interseptovalvulare was sometimes seen. Often bands of tissue bridged the atrial cavity.

There was a fossa ovalis type of atrial septal defect (Fig. 1a), often with a straddling inferior vena cava, in all but two cases. In one exceptional case there was a sinus venosus defect, and in one an absence of the atrial septum. In two cases there was an aneurysm of the fossa ovalis that bulged into the left atrium.

The right ventricle was enlarged in most cases with a wall that was either normal or thicker or thinner than normal. The right ventricle consisted mostly of a greatly enlarged sinus with a relatively small conus (Fig. 1b). The region adjacent to the medial leaflet of the tricuspid valve was smooth with no chordae or papillary muscles (Fig. 1a). There was an abnormally formed large parietal band with an underdeveloped septal band forming a shallow arch (Fig. 1b). The pulmonary trunk, although smaller than normal, was of surprisingly good size in view of the pulmonary atresia.

The left atrium and ventricle were usually hypertrophied and enlarged with normal or thickened walls. The mitral valve orifice was usually enlarged but was normal in some cases. The mitral valve was normal in structure but in a few cases showed increased hemodynamic change.* The ventricular septum was intact in all cases. The aortic orifice was usually enlarged but in some cases it was normal in size. The ductus arteriosus was patent in all cases but small in diameter in two.

Aside from the abnormalities in the right atrium there were no associated cardiac abnormalities. The situs of the organs was normal in all cases. The spleen was normal in all but one case in which there was an accessory spleen. Multiple extracardiac abnormalities were found in six cases.

Discussion

Pulmonary atresia with tricuspid insufficiency is a relatively rare anomaly. At the Congenital Heart Disease Research and Training Center, in 4,250 cases of congenital heart disease there were 15 cases of pulmonary atresia with tricuspid insufficiency compared with 136 cases of pulmonary atresia with tricuspid stenosis. There has been a tendency to group these two anomalies together as type I, pulmonary atresia with intact ventricular septum (pulmonary atresia with tricuspid stenosis), and type II, pulmonary atresia with tricuspid insufficiency. This practice is justified if one considers the pulmonary atresia and the intact ventricular septum

* The term "increased hemodynamic change" implies that at the gross level the entire valve is equally thickened with slightly thickened chordae, more so than in the same valve of a normal heart of a person of the given age. This observation is always made with a control valve before the observer. As a valve ages it becomes thickened because of hemodynamic changes (McMillan and Lev).[39] This change is increased in some valves in patients with congenital heart disease because of altered hemodynamics. This change is easily differentiated grossly from an inflammatory valve, which shows irregularity in thickness at the line of closure and the edge with irregular thickness and fusion of the chordae.

FIGURE 3. Tricuspid valves. **a,** of a 35 hour old normal child; **b,** of a 35 hour old child with pulmonary atresia with tricuspid insufficiency, basal part; **c,** same as **b** but peripheral portion; **d,** of a 1 day old child with pulmonary atresia with tricuspid stenosis (basal portion); **e,** same as **d** but peripheral portion. F = fibrosa; P = proximalis (elastified); S = spongiosa. (Wetzel-Lee Glasser X20, reduced by 25 percent.)

the dominating themes in these anomalies. However, there are great morphologic differences between the two entities.

Morphologic differences in pulmonary atresia with tricuspid stenosis versus tricuspid insufficiency: In pulmonary atresia with tricuspid stenosis (type I) there is a small or minute tricuspid orifice, with a valve that on gross inspection is normal in size or shortened but thickened with a slight downward displacement in some cases. In pulmonary atresia with tricuspid insufficiency, gross inspection reveals a distinctly abnormal valve with abnormal leaflets. The anterior leaflet is large with nodular formations; it is often sail-like, with abnormal chordal and papillary muscle attachments, and reminiscent of the leaflet seen in Ebstein's disease. The medial leaflet is either absent or thickened and tethered to the wall with no chordal attachment at the edge. This gives a peculiarly smooth appearance to the right ventricular septal wall. The inferior leaflet is often large, and again nodular, with a small papillary muscle.

Histologic examination of the valve in the two entities also shows some differences. The valve leaflets are greatly enlarged in pulmonary atresia with tricuspid insufficiency. There is more disorganization in the valve in this entity with alternating thick and thin areas consisting in some cases of fibrosa alone, or of mostly spongiosa, or of both elements. In contrast, the valve in pulmonary atresia with tricuspid stenosis shows a more organized valve with a fibrosa generally thicker than normal and a variable amount of spongiosa. There is no difference in the hypoelastification of the periphery seen in congenitally abnormal valves.[40] It may be argued that the differences in the valves in these two entities are a hemodynamic function of the size of the tricuspid orifice and right ventricle. We cannot answer this question from our present knowledge; nevertheless there is a distinct difference in the morphology of the two valves.

The right ventricle in the two conditions is quite dissimilar. In tricuspid stenosis with pulmonary atresia there is a small right ventricle with a thick wall and endocardial fibroelastosis; it consists of a small conus and markedly attenuated sinus. In tricuspid insufficiency with pulmonary atresia the right ventricle is huge in most cases and consists mostly of an abnormal and large sinus. The muscle of Lancisi, if present, is high and the conus is relatively small, with a large parietal band and a smaller septal band forming a shallow arch beneath the pulmonary trunk (Fig. 1b).

Surgical implications of anatomic differences: The morphologic differences between the two entities are reflected in the results of the surgical treatment of pulmonary atresia with tricuspid insufficiency. Whereas the results with a shunt or a shunt combined with a Brock procedure have been satisfactory in only a few cases of pulmonary atresia with tricuspid stenosis, such treatment has been more favorable in pulmonary atresia with tricuspid insufficiency.[10,12,13,18,19,21,23,25–27,29,30,32,34–36] In the latter, the two procedures might be combined with atrial septostomy and plication of the tricuspid valve to give better results. This type of combined procedure might carry the patient over to an age when replacement of the tricuspid valve by a prosthetic valve combined with a Rastelli procedure may be beneficial; or closure of the tricuspid orifice may be combined with a right ventricular bypass from the right atrium to the pulmonary trunk.

Differentiation from Ebstein's disease of the tricuspid valve: The concept of separation of the entity pulmonary atresia with tricuspid insufficiency from pulmonary atresia with tricuspid stenosis was previously espoused by Barr et al.[35] on clinical and pathologic grounds. Pulmonary atresia with tricuspid insufficiency is closer pathologically to Ebstein's disease with pulmonary atresia, congenital isolated tricuspid insufficiency and congenital absence of the tricuspid valve. When in pulmonary atresia with tricuspid insufficiency there is absence of part of the medial leaflet and when fragments of valve are found in the right ventricle more distally, it is difficult to separate this entity from Ebstein's disease. The normally placed inferior leaflet suggests the presence of pulmonary atresia with tricuspid insufficiency.

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Altered Hemoglobin-Oxygen Affinity With Long-Term Propranolol Therapy in Patients With Coronary Artery Disease

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Pharmacologic agents that alter hemoglobin affinity for oxygen may affect systemic or myocardial oxygen delivery. In vitro, and in normal man, propranolol shifts the oxyhemoglobin equilibrium curve to the right, thus increasing the partial pressure of oxygen at which hemoglobin is 50 percent saturated (P_{50}) and enhancing oxygen delivery. The effect of propranolol on hemoglobin P_{50} was evaluated in 12 patients with angina pectoris and documented coronary artery disease. Determinations were made during oral propranolol therapy (mean daily dose 152 mg) of at least 3 months' duration and after administration of propranolol had been discontinued for at least 4 days. Hemoglobin P_{50} and erythrocyte 2,3-diphosphoglycerate (DPG) were measured. Data in 12 patients were: the mean P_{50} after discontinuation of propranolol was 28.2 mm Hg ± 0.9 (standard error of the mean) and during propranolol therapy 31.7 ± 0.7; $P < 0.001$; red blood cell 2, 3-DPG did not change to explain the increase in P_{50}. This demonstrated shift could increase systemic oxygen delivery and thus benefit marginally perfused myocardium while sparing coronary flow. Propranolol, in addition to its negative chronotropic and inotropic effects, may increase tissue oxygen delivery in patients with the anginal syndrome.

Decreased hemoglobin affinity for oxygen, reflected in a right shift in the oxyhemoglobin equilibrium curve, results in increased oxygen delivery to tissues. Increased erythrocyte 2,3-diphosphoglycerate is one means by which the oxyhemoglobin curve is shifted to the right.[1-3] Recently, rightward-shifted curves with increased 2,3-diphosphoglycerate have been found in several clinical states: systemic hypoxia at high altitude,[3] cyanotic congenital heart disease,[4] congestive heart failure,[5] anemia[6] and chronic lung disease.[7] Certain drugs—inosine,[8] androgens,[9] aldosterone and cortisol[10] and triiodothyronine[11]—have been reported to increase 2,3-diphosphoglycerate. Recently propranolol, added to a red cell suspension[12] and administered to a group of apparently normal persons,[13] has been found to shift the oxyhemoglobin curve to the right without a quantitative change in total 2,3-diphosphoglycerate.

These studies have posed the possibility of a new pharmacologic approach to clinical states manifested by ischemia. In patients with the anginal syndrome a rightward-shifted hemoglobin oxygen curve might (1) enhance oxygen delivery to marginally perfused myocardium, (2) improve systemic tissue oxygenation, and (3) maintain systemic oxygen delivery at a lower level of cardiac output. This study was designed to determine the effect of propranolol on hemoglobin-oxygen affinity in patients with documented coronary artery disease.

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TABLE I

Summary of 12 Cases

Case no.	Age(yr) & Sex	Clinical Class Angina	Prior MI	Resting ECG	Dose of Propranolol (mg/day)	Other Med	LVEDP	CI	O_2 Sat (%) PA	O_2 Sat (%) Ao	LV Angio	Coronary Vessels (>75% stenosis)	Chest X-ray Film	Smoking History
1	63F	III	SEMI, 1973	N	30	NTG, iso	12	...	...	...	Abn	RCA, LAD, LCx	N	None
2	52M	III	No	↓T wave (III)	160	Iso	25	1.8	71	93	Abn	RCA, LAD, LCx	N	Stopped 4 yr
3	48M	III	IWMI, 1965	Old IWMI	70	NTG, iso	14	2.3	76	95	Abn	RCA, LAD, LCx	↑LV	Stopped 3 wk
4	36M	II	No	N	160	NTG	12	3.2	81	96	N	LAD	N	Stopped 3 yr
5	43M	II	No	↓T wave (aVL)	160	NTG	12	2.0	...	...	N	LAD, LCx	N	Stopped 3 mo
6	46F	II	No	↓T wave (aVL)	160	NTG, iso, dipyr	12	2.8	82	96	N	LAD	N	None
7	41M	IV	No	N	160	NTG, iso	12	2.4	75	95	N	RCA, L main LAD, LCx	N	Stopped 3 wk
8	51M	III	ASMI, 1972	Old ASMI	160	NTG, iso, quin	16	1.8	74	95	Abn	RCA, LAD	↑LV	None
9	49M	II	No	N	120	NTG, iso	12	...	...	...	Abn	RCA, LAD	N	0.5 pack/day
10	54F	III	SEMI, 1971	↓S-T, T waves I, aVL, V_{5-6})	240	NTG, dig, proc	10	2.7	76	95	N	LAD	N	None
11	36M	II	IWMI, 1970?	Old IWMI	240	NTG	12	2.8	...	...	N	LAD, RCx	N	Stopped 1.5 yr
12	55M	III	No	↓T wave (V_{1-4})	160	Iso	16	3.3	77	99	N	RCA, LAD	Sl ↑ vasc markings	Stopped 1 mo

↓ = decreased; ↑ = increased or enlarged.

Abn = abnormal; Angio = angiogram; Ao = aorta; ASMI = anteroseptal myocardial infarction; CI = cardiac index (liters/min per m^2); dig = digoxin; dipyrid = dipyridamole; ECG = electrocardiogram; iso = isosorbide dinitrate; IWMI = inferior wall myocardial infarction; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure (mm Hg); Med = medication; MI = myocardial infarction; N = normal; NTG = nitroglycerin; PA = pulmonary artery; proc = procainamide; quin = quinidine; RCA = right coronary artery; RCx = right circumflex coronary artery (anomalous); Sat = saturation; SEMI = subendocardial myocardial infarction; Sl = slightly; vasc = vascular.

Methods

Protocol: Twelve patients with stable angina pectoris were studied during oral propranolol therapy of at least 3 months' duration. The patients received an average of 152 mg/day (range 40 to 240) divided in four doses. In each patient the dose used was that which produced a resting bradycardia and, in some cases, partial relief of angina. The study procedures were explained fully to the patients, who gave informed written consent. Arterial and venous blood samples were obtained 2 hours after the most recent dose of propranolol. Administration of propranolol was then discontinued for at least 4 days, and arterial and venous blood samples were again obtained under identical conditions. Each patient, therefore, served as his own control. The biologic half-life of propranolol is 2.5 to 5 hours during long-term oral therapy.[14–17]

The following determinations were performed: venous partial pressure of oxygen (PO_2) at which hemoglobin is 50 percent saturated with oxygen at pH 7.40, 37°C, erythrocyte 2,3-diphosphoglycerate, hemoglobin, hematocrit, mean corpuscular volume, potassium, phosphorous, arterial PO_2, partial pressure of carbon dioxide (PCO_2) and pH. Arterial and peripheral venous P_{50} and 2,3-diphosphoglycerate do not differ significantly.[18]

Patient population: The clinical, hemodynamic and angiographic characteristics of the 12 patients studied are summarized in Table I. All patients were in functional classes II to III (class I was defined as no limit to physical activity, class II as angina with strenuous activity, class III as angina with mild normal daily activity and class IV as angina at rest). Five patients had had a prior myocardial infarction, but none more recently than 1 year before study. Most patients took sublingually administered nitroglycerin and "long-acting" nitrates throughout the study without change in dose. One patient was taking digoxin and a diuretic agent.

No patient had clinical signs of congestive heart failure, valvular or congenital heart disease or historical or roentgenographic evidence of pulmonary disease. None had had a recent blood transfusion. Only one patient was currently smoking (0.5 pack of cigarettes/day) when studied with and without propranolol. All had normal blood urea nitrogen levels and thyroid function tests.

All patients had coronary arteriography within 1 month of the study because of severe angina pectoris despite medical therapy. All proved to have at least a 75 percent stenosis of the luminal diameter of one or more major coronary vessels. Before arteriography, cardiac output was determined in 10 patients by the indocyanine green dye-dilution method or by the Fick technique. In 7 of the 10, the cardiac index was within normal limits (greater than 2.3 liters/min per m^2). Only four patients had elevated left ventricular diastolic filling pressure (greater than 12 mm Hg.) No patient had arterial oxygen desaturation or abnormally decreased mixed venous oxygen saturation at rest.

TABLE II

Blood Studies in 12 Patients Without (numerator) and With (denominator) Propranolol Therapy

Case no.	P_{50}	2,3-DPG	Hb	Hct	MCV	PO_2	pH	PCO_2	K	Phos
1	29.8	5.42	11	33	90	90	7.44	34	4.2	3.6
	36.7	6.14	11	32	88	96	7.40	36	4.8	3.6
2	25.7	3.72	14	43	85	81	7.39	36	4.0	3.2
	31.9	4.23	14	41	84	81	7.40	40	4.3	4.1
3	24.0	3.70	15	43	...	99	7.41	39	...	...
	29.5	2.87	15	44	...	...	...	...	...	2.9
4	22.9	4.36	14	42	89	90	...	...	...	...
	27.9	4.27	14	44	88	89	7.44	40	...	3.7
5	27.9	4.30	14	44	87	95	7.46	36	4.0	3.2
	32.0	5.41	12	36	90	98	7.43	36	4.5	3.2
6	30.8	5.59	13	40	88	90	7.46	38	3.5	2.8
	34.6	5.88	13	39	85	94	7.44	37	3.7	3.2
7	26.7	4.36	13	39	92	81	7.40	41	...	4.9
	30.0	4.11	15	42	92	90	...	...	...	3.8
8	26.8	4.72	16	47	96	75	7.45	27	4.0	3.8
	29.0	4.20	16	48	94	90	7.43	34	4.2	3.3
9	29.7	4.49	13	41	95	80	7.43	39	4.1	3.2
	31.8	5.01	14	43	93	94	7.39	...	4.3	4.3
10	31.0	5.09	11	33	...	76	7.45	40	...	3.5
	33.0	4.89	10	31	94	87	7.43	36	4.0	4.3
11	30.4	3.97	16	48	91	80	7.44	...	...	...
	31.6	4.01	16	48	...	...	...	...	...	...
12	32.3	4.38	14	44	90	96	7.43	36	4.6	3.3
	31.8	3.89	14	44	91	95	7.37	33	4.0	4.0
Mean	28.2	4.5	13.7	41.4	90.3	86.1	7.4	36.6	4.1	3.5
± SEM	± 9	± 0.2	± 0.5	± 1.4	± 1.1	± 2.3	± 0	± 1.3	± 0.1	± 0.2
	31.7	4.6	13.7	41.0	89.9	91.4	7.4	36.5	4.2	3.7
	± 0.7	± 0.3	± 0.5	± 1.6	± 1.1	± 1.6	± 0	± 0.9	± 0.1	± 0.1
*P**	<0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS

**P* (probability) value calculated with paired *t* test.

2,3-DPG = 2,3 diphosphoglycerate (μmol/ml red blood cell); Hb = hemoglobin (g/100 ml); Hct = hematocrit (percent); K = serum potassium (normal = 3.6 to 4.6 mEq/liter); MCV = mean corpuscular volume of the erythrocyte (ml); NS = not significant; P_{50} = partial pressure of oxygen at 50 percent saturation of hemoglobin (mm Hg); PCO_2 = partial pressure of carbon dioxide; Phos = serum inorganic phosphorus (normal 3.1 to 4.5 mg/100 ml); PO_2 = partial pressure of oxygen; SEM = standard error of the mean.

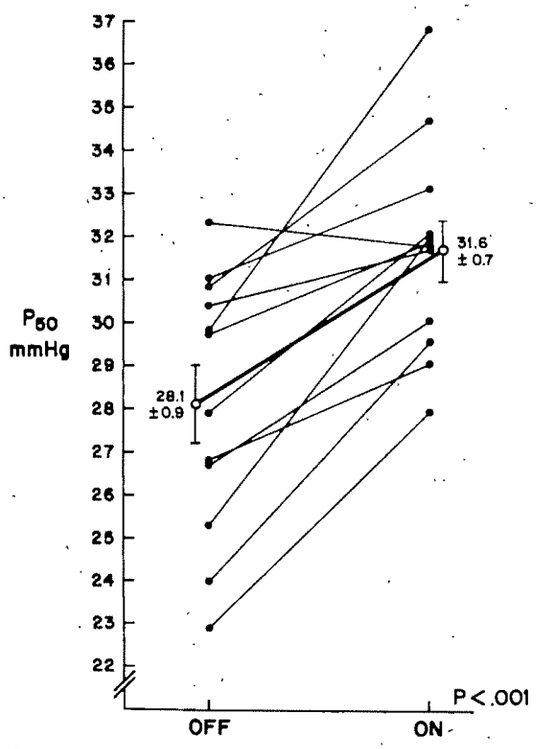


FIGURE 1. P_{50} with and without propranolol. The mean P_{50} increased from 28.2 mm Hg ± 0.9 (standard error of the mean) when the 12 patients were not taking propranolol (OFF) to 31.7 ± 0.7 during propranolol therapy (ON). This 3.5 mm Hg increase reflects a rightward shift of the oxyhemoglobin equilibrium curve with propranolol therapy. P = probability.

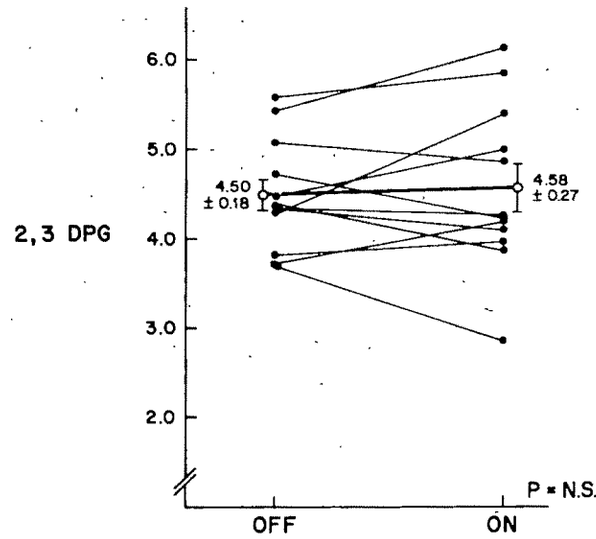


FIGURE 2. 2,3-diphosphoglycerate with and without propranolol. The rightward shift of the oxyhemoglobin curve during propranolol therapy was not due to a change in erythrocyte 2,3-diphosphoglycerate (DPG) values (expressed in μmol/ml), which were normal whether patients were (ON) or were not (OFF) receiving propranolol. N.S. = not significant; P = probability.

Methods of analysis: Determinations of P_{50} and 2,3-diphosphoglycerate were begun on heparinized blood within 10 minutes after the sample was obtained. Hemoglobin affinity for oxygen was measured with the mixing technique[19] and the result expressed as the partial pressure of oxygen in millimeters of mercury when 50 percent of the hemoglobin is saturated with oxygen at pH 7.40, 37° C. An increase in P_{50} reflects a rightward shift in the oxyhemoglobin curve. The standard deviation of repeated measurements of the same blood in our laboratory is 1.6 mm Hg. Erythrocyte 2,3-diphosphoglycerate was measured with the Sigma kit using the stoichiometric oxidation of reduced nicotinamide adenine dinucleotide (NADH) to NAD according to the method of Keitt.[20] The reproducibility of determinations in the same blood in our laboratory is 0.6 μmol/ml of erythrocyte.

Arterial blood PO_2, PCO_2 and pH were measured using a Radiometer Acid-Base Analyzer PHM71. Serum inorganic phosphorous was measured with the method of Goldenberg and Fernandez.[21] Hemoglobin was assayed as the cyanmethemoglobin derivative and mean corpuscular volume and erythrocyte count was measured directly with the Coulter Counter model S. Hematocrit was calculated with the Coulter method and also determined directly using microcentrifugation. Serum potassium was measured with standard methods.

Multistage submaximal exercise testing using an electronically braked bicycle ergometer was performed in seven patients during and after propranolol therapy. A modified four lead electrocardiogram (inverted aVF, V_2, V_4 and V_6) was recorded each minute, and blood pressure every 4 minutes. The end points were: angina, marked dyspnea or fatigue, hypotension, greater than 1 mm horizontal S-T segment depression, S-T elevation or arrhythmia.

All data were compared with use of a paired *t* test.

Results

The mean P_{50} (pH 7.40) was 28.2 mm Hg ± 0.9 (standard error of the mean) when propranolol was withdrawn and 31.7 mm Hg ± 0.7 while the patients were taking propranolol ($P < 0.001$) (Table II, Fig. 1). Eleven patients had an increase in P_{50} (range 1.2 to 6.9 mm Hg) and one patient had no significant change. The increase in mean P_{50} of 3.5 mm Hg induced by propranolol represents a significant shift to the right in the oxyhemoglobin equilibrium curve.

The increase in P_{50} was not associated with an increase in erythrocyte 2,3-diphosphoglycerate (Fig. 2); the mean value without propranolol therapy was 4.50 μmol/ml erythrocyte ± 0.2 and during drug administration it was 4.6 ± 0.3 (difference not significant).

All other blood studies for factors reported to alter 2,3-diphosphoglycerate or P_{50} were normal or unchanged throughout the study. These included arterial PO_2, pH, PCO_2, inorganic phosphorous and hemoglobin concentration. Mean corpuscular volume and plasma potassium concentration were likewise unchanged (Table II). Two patients had mild normocytic anemia (hemoglobin AA) that was unchanged throughout both phases of the study. PO_2 determinations were above 80 mm Hg except for one value of 75 and one of 76, both noted after withdrawal of propranolol. These levels probably did not affect the diphosphoglycerate measurements because the threshhold for activation of the latter has been shown to be 60 mm Hg.[9] Moreover, these two patients had normal PO_2 values (90 and 87 mm Hg) while taking propranolol.

TABLE III

Results in Seven Patients Who Underwent Exercise Testing

Patient no.	ΔP_{50}	Maximal Resistance	
		Without Propranolol	With Propranolol
1	+6.9	0	50
2	+6.2	50	75
3	+5.5	50	100
5	+4.1	75	75
6	+3.8	50	50
8	+2.2	75	50
12	−0.6	100	75

ΔP_{50} = P_{50} during propranolol therapy minus P_{50} without propranolol (mm Hg); *maximal resistance* = work load (in watts), on bicycle ergometer when exercise was terminated because of angina.

The three patients with a substantial increase in P_{50} (5.5, 6.6, 6.9 mm Hg, respectively) had significantly increased exercise tolerance as determined with exercise testing (Table III). Two patients with a less marked increase in P_{50} (3.8 and 4.1 mm Hg, respectively) had no objective change in exercise tolerance. One patient with a minimal change (2.2 mm Hg) and one with a decrease in P_{50} (−0.6 mm Hg) had decreased exercise tolerance.

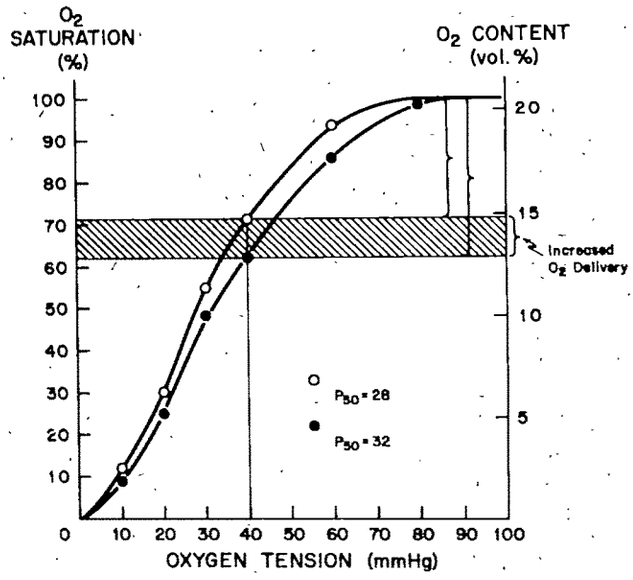


FIGURE 3. Theoretical increase in oxygen delivery due to shift to the right of the oxyhemoglobin curve. If one assumes a normal mixed venous PO_2 of 40 mm Hg, if the oxyhemoglobin curve shifts to the right (increased P_{50}) by 3.5 mm Hg, the arteriovenous oxygen difference widens from 5.46 to 7.56 ml O_2/100 ml, an increase of 38.5 percent in oxygen delivery (see text). **Closed** and **open circles** indicate, respectively, P_{50} values without and with propranolol therapy.

Discussion

Mechanism of effects of propranolol on oxyhemoglobin dissociation: This study documents a rightward-shifted oxyhemoglobin dissociation curve in patients with coronary artery disease receiving long-term oral propranolol therapy. The data follow previous in vitro studies that support such an action of propranolol. Three mechanisms have been proposed to explain these observations:

1. In red cell suspensions, Oski et al.[22] found that approximately 30 percent of 2,3-diphosphoglycerate may be normally bound to red blood cell membranes, and therefore may be incapable of binding to deoxyhemoglobin. They reported that propranolol administered in vitro released membrane-bound diphosphoglycerate. This, they postulated, then combined with deoxyhemoglobin and increased P_{50}.[22] However, others[23] have not found any 2,3-diphosphoglycerate bound to the erythrocyte membranes.

2. On the basis of in vitro studies by Manninen[24] and Agostoni et al.[25] it was reported that propranolol added to a red cell suspension has a direct effect on the cell membrane leading to an altered Gibbs-Donnan equilibrium and a decrease in intra-erythrocyte pH. By the classic Bohr effect this would shift the oxyhemoglobin equilibrium curve to the right. In a red cell suspension, a decrease in mean corpuscular volume and an increase in potassium concentration of the medium occur when propranolol acts on the red cell membrane.

3. Finally, the rightward-shifted oxyhemoglobin dissociation curve of patients receiving propranolol may be a compensation for the decrease in myocardial contractility and decrease in cardiac output associated with administration of propranolol. Compensation for arterial hypoxemia or tissue ischemia would be expected to occur through increased 2,3-diphosphoglycerate.[4–6] However, no patients in our study manifested any change in the latter or any evidence of congestive heart failure.

Not all reported data confirm a shift to the right of the oxygen-hemoglobin dissociation curve by propranolol. Lichtman et al.,[26] on the basis of studies in six normal subjects and two patients, concluded that propranolol had no significant effects on P_{50}. Their studies in normal subjects were performed before, and then 4 and 24 hours after, administration of a single dose of propranolol. Thus they were attempting to measure an acute effect, as opposed to the long-term changes measured in our study. The two patients studied had been receiving larger doses for long periods. Their P_{50} data were expressed as "within 1 standard deviation" of the normal mean. In our study, patients were studied both with and without propranolol. Thus, each patient served as his own control.

Significance of the shifted oxyhemoglobin curve: The determinants of tissue oxygen delivery include the hemoglobin concentration, the partial pressure of oxygen (which determines the amount of oxygen dissolved in plasma), tissue blood flow and the affinity of hemoglobin for oxygen. Changes in any one of these variables will affect the amount of oxygen delivered to tissues. Decreased hemoglobin affinity for oxygen permits increased oxygen delivery to tissues and therefore may offer benefit in ischemic states.

In our patients with documented coronary artery disease propranolol caused an average 3.5 mm Hg increase in hemoglobin P_{50}, thus indicating a significantly

rightward-shifted oxyhemoglobin curve and representing decreased hemoglobin affinity for oxygen.

Figure 3 illustrates the theoretical increase in oxygen delivery to tissues that would be produced by a shifted oxyhemoglobin curve of the magnitude associated with propranolol therapy in our study. As the P_{50} of the hemoglobin-oxygen equilibrium curve shifts to the right by 3.5 mm Hg (28.2 to 31.7), the oxygen content of blood at a normal mixed venous PO_2 of 40 mm Hg would decrease from 14.9 to 12.8 volumes percent. Assuming a normal oxygen capacity of 21 volumes percent and an arterial oxygen saturation of 97 percent, the unshifted curve would achieve an arteriovenous oxygen difference of 5.46 ml O_2/100 ml of blood flow, while the rightward-shifted curve associated with propranolol therapy would achieve an arteriovenous difference of 7.56 ml O_2/100 ml of blood flow. The increase in oxygen delivery to tissues would be 2.10 ml O_2/100 ml of blood flow. This represents a 38.5 percent increase in systemic oxygen delivery at a given cardiac output:

$$\frac{2.10 \text{ volume percent}}{5.46 \text{ volume percent}} \times 100 = 38.5 \text{ percent}$$

Or, a given level of systemic oxygen delivery could be effected by a lower cardiac output.

The increase in oxygen delivery produced by a rightward-shifted hemoglobin-oxygen dissociation curve at the usual low coronary sinus PO_2 of about 20 mm Hg would be less than in other venous beds that function at a higher PO_2 level, but would be similar in direction. Because there is a gradient of oxygen tension from subepicardium to subendocardium, and because coronary artery disease is a heterogeneous phenomenon, the exact increase in regional myocardial oxygen delivery would be variable. However, at any tissue PO_2 level, there would be some increase in oxygen unloading due to a rightward-shifted oxyhemoglobin curve. The measurable effects of such a shift would be difficult to predict. If myocardial oxygen demands were held constant, one might anticipate a decrease in coronary flow and an increase in the percent of arterial oxygen extracted by the myocardium. Wolfson and Gorlin,[27] after an infusion of propranolol in patients with coronary disease, reported a reduction in coronary flow, and an increase in myocardial oxygen extraction. Mueller et al.[28] reported a decrease in myocardial oxygen extraction when propranolol was administered intravenously to patients during the course of an acute myocardial infarction.

In our seven patients who performed exercise tests, the larger increases in P_{50} were associated with increased exercise tolerance while they were taking propranolol, thus suggesting that the rightward-shifted curves may have contributed to improved performance. The exercise tests were performed first during propranolol therapy, then after propranolol was withdrawn. Thus, any improvement due to a training effect[29] would have minimized the changes observed. Of course, a major part of the beneficial effect of propranolol upon exercise performance would be expected to be due to reduced myocardial oxygen demands during exercise, as demonstrated by Wolfson and Gorlin.[27]

Implication: Orally administered propranolol shifted the oxyhemoglobin equilibrium curve to the right in our 12 patients with moderate to severe angina pectoris. No change in 2,3-diphosphoglycerate occurred. This shift may account for part of the therapeutic effect of this drug. Moreover, the drug may be a prototype for pharmacologic manipulation of hemoglobin-oxygen affinity as therapy of patients with ischemic states.

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Effects of Propranolol on the Hemodynamic, Coronary Sinus Blood Flow and Myocardial Metabolic Response to Atrial Pacing

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The hemodynamic, coronary sinus blood flow and myocardial metabolic effects of 0.15 mg/kg body weight of intravenously administered propranolol were studied in 19 patients with coronary artery disease and 6 normal patients. Atrial pacing was performed in all patients and produced angina in 15 of the 19 patients with coronary artery disease. In these patients propranolol reduced heart rate from 78 to 69 beats/min, cardiac index from 3.0 to 2.6 liters/min per m^2 and left ventricular stroke work index from 47 to 43 g-m/m^2; it increased total peripheral resistance from 24 to 28 units and lactate extraction from 16.3 to 22.5 percent. There was no significant change in mean arterial pressure, left ventricular end-diastolic pressure, coronary sinus blood flow or myocardial oxygen consumption. During a second pacing stress propranolol produced clinical improvement in 9 of the 15 patients who experienced angina initially. The improvement was associated with less severe abnormalities in S-T depression and left ventricular end-diastolic pressure, increased lactate extraction and no significant change in coronary sinus blood flow or myocardial oxygen consumption. Thus, propranolol appears to be capable of modifying the anginal threshold as determined with atrial pacing, and the clinical response appears to be independent of global changes in coronary sinus blood flow and myocardial oxygen consumption.

Despite widespread use and study of the beta adrenergic blocking agent propranolol in therapy for ischemic heart disease, its precise mechanism of action remains unclear. It is known to exert an influence on various sites in the cardiovascular system with a resultant decrease in heart rate, myocardial contractility and blood pressure and an increase in ventricular volume.[1–3] Little information exists concerning direct measurements of coronary blood flow or myocardial oxygen consumption.[4,5] The beneficial effects of propranolol in ischemic heart disease have been attributed to an overall reduction in oxygen consumption of the heart produced by a favorable balance between these complex opposing factors.[5–7]

This study was designed to (1) test the therapeutic efficacy of an intravenous bolus injection of propranolol on the anginal threshold as assessed with atrial pacing; (2) examine the effects of the drug on systemic and coronary hemodynamics, myocardial lactate metabolism and oxygen consumption; and (3) assess which component of the net effect of propranolol is attributable to its negative chronotropic influence.

Methods

Patients: Twenty-five patients were studied during routine diagnostic cardiac catheterization for the investigation of known or suspected coronary artery disease. Six of the 25 had normal coronary arteries and were studied because of chest pain. None of the six had a cardiac murmur or evidence of mitral valve prolapse; one had an abnormal treadmill exercise test. Nineteen patients had coronary artery disease as defined by a 75 percent or greater narrowing of luminal diameter in one or more major coronary vessels. All were in the fasting state and

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TABLE I

Study Protocol

1. Control A
2. Pace
3. Control B
4. Propranolol
5. Propranolol-Pace Control (rate restored to that in Control B)
6. Propranolol-Pace (rate achieved to match that in Pace)

had received 5 to 10 mg (dose based on body weight) of diazepam orally approximately 120 to 150 minutes before the initial control measurements.

Measurements: Under local anesthesia a no. 9 double lumen Goodale-Lubin catheter was passed from the right antecubital fossa into the right side of the heart so that its tip lay in the pulmonary artery and its proximal lumen in the right ventricle. A no. 7 or 8 angiographic catheter was introduced into the left ventricle by way of an arteriotomy in the right brachial artery, and a Teflon® cannula was inserted into the left brachial or radial artery with the Seldinger technique. Pressures were measured from the left ventricle and systemic artery over at least two respiratory cycles, and the mean systemic arterial pressure was obtained electronically.

Through the cephalic or basilic vein from the left antecubital fossa, a no. 7 catheter was placed in the coronary sinus. This catheter was modified for the measurement of coronary sinus blood flow with the thermal dilution technique described by Ganz et al.[8] Two thermistors are mounted on the catheter, an internal one located near the orifice for the measurement of injectate temperature and an external one located 2 cm proximal to the tip for the measurement of coronary sinus blood temperature. The catheter contains two electrodes, one at its tip and a second one 2.5 cm proximally for the purpose of atrial pacing. It also has a lumen to permit blood sampling through an orifice situated on the inner curve 0.5 cm from the tip. Coronary sinus blood flow measurement involves infusion of 5 percent dextrose in water at room temperature into the coronary sinus with a Harvard infusion pump at a constant rate of 40 to 50 ml/min. The exact rate is calibrated for each catheter and connecting tubing. The measurement relies upon the fact that after the infusion the resultant decrease in coronary sinus blood temperature is inversely related to the rate of flow and this is expressed mathematically as

$$\text{Coronary sinus blood flow} = \left\{\frac{T_B - T_I}{T_B - T_M}\right\} - 1 \times 1.08$$

where F_I = the rate of injectate (ml/min) and T_B, T_I, T_M = the temperatures in degrees centigrade of blood, injectate and mixture of blood and injectate, respectively. Special attention was given to placing the catheter in a stable position so that its tip lay in the mid portion of the coronary sinus and its external thermistor was situated inside the orifice and proximal to the posterior interventricular vein. This was confirmed with the injection of contrast medium at both the beginning and the end of the procedure.

Coronary sinus blood flow measurements over the 60 to 90 minute study period required the intermittent infusion of 250 to 300 ml of 5 percent dextrose and water. To evaluate the possible role of this infusion, five additional studies were performed in patients with coronary artery disease according to a protocol identical to that in Table I except that propranolol was not administered. In addition to lactate determinations, arterial blood glucose measurements were also made in this group of patients.

During a 10 minute period, lead II of the electrocardiogram and pressures from the left ventricle and brachial or radial artery were recorded at frequent intervals. The cardiac output was measured, at least in duplicate, during the terminal portion of the control period with the dye-dilution technique using indocyanine green with injection into the right ventricle and sampling from the systemic artery. Reinfusion of the withdrawn blood was performed after each determination.

Protocol (Table I): Control hemodynamic measurements (Control A) were made and followed immediately by determination of coronary sinus blood flow and arterial and coronary sinus sampling for oxygen content* and lactate analysis. Atrial pacing (Pace) was then commenced at a rate approximately 25 percent above the control sinus rate and the pacing rate increased by 10 beats/min at intervals of 3 minutes until angina developed or a rate of 150 beats/min was achieved. Once angina occurred or the maximal rate was achieved, measurements of cardiac output, coronary sinus blood flow and sampling for oxygen content and lactate were performed. Pacing was then discontinued and after a recovery period of 10 to 15 minutes a second control set of observations was recorded (Control B). Propranolol, 0.15 mg/kg body weight, was then administered intravenously over 5 minutes and pressures were measured 5 and 10 minutes after drug administration and all hemodynamic and metabolic measurements were repeated after 15 minutes (Propranolol). Heart rate was then restored, by atrial pacing if necessary, to the level observed during the second control period and the measurements were repeated (Propranolol-Pace Control). Atrial pacing was then reinstituted to replicate precisely the original pacing stress (Propranolol-Pace). The total amount of blood required for metabolic studies was 35 to 40 cc.

In seven patients (four with coronary artery disease and three with normal arteries) the maximal rate during the initial pacing period was limited by the development of Wenckebach atrioventricular (A-V) block. Pressures were measured continuously and pacing was interrupted for 10 to 15 second intervals after 1 and 3 minutes of pacing at each rate to assess the change in left ventricular end-diastolic pressure and S-T segments during a sudden reduction in heart rate.

Patients were instructed to report if any chest pain, tightness or discomfort occurred. Care was taken to identify as angina those symptoms that simulated the patients' clinical complaints. Fifteen of the 19 patients with coronary artery disease experienced discomfort during the initial pacing period; these 15 were then further classified into groups that did (no. = 9) and did not (no. = 6) show improvement during pacing after administration of propranolol. Improvement was defined as clear-cut delay in the onset of angina (three patients) or marked diminution in its intensity or its abolition (six patients) during the second pacing period.

Derived calculations were performed using the formulas:

$$SI = \frac{CI}{HR}, \quad LVSWI = \frac{(MAP - LVEDP) \times SI \times 13.6}{1000},$$

$$TPR = \frac{MAP}{CO}, \quad CVR = \frac{MAP}{CSBF} \text{ and } MVO_2 = CSBF \times (\text{arterial} - \text{coronary sinus}) O_2 \text{ content},$$

where SI = stroke index (ml/beat per m^2), CI = cardiac index (liters/min per m^2), HR = heart rate (beats/min); LVSWI = left ventricular stroke work index (g-m/m^2), MAP = mean arterial pressure (mm Hg), LVEDP = left ventricular end-

* Automated determination using Lex-O_2-Con Lexington Instruments, Waltham, Massachusetts.

TABLE II

Summary of Systemic and Coronary Hemodynamics and Metabolic Data in 6 Normal Subjects and 19 Patients With Coronary Artery Disease

	HR (beats/min)	MAP (mm Hg)	LVEDP (mm Hg)	CI (liters/min per m^2)	SI (ml/beat per m^2)	LVSWI (g-m/m^2)	TPR (units)	Lactate (% extraction)	Art Lactate (mg/100 ml)	CS Lactate (mg/100 ml)	CSBF (ml/min)	CVR (units)	MVO_2† (ml/min)	(Art-CS) O_2† (ml/100 ml)
A. Normal Subjects														
CT A	76 ± 4	102 ± 7	12 ± 2	3.7 ± 0.3	48 ± 4	60 ± 7	26 ± 2	22.5 ± 4.6	7.6 ± 1.3	5.7 ± 0.8	151 ± 15	0.71 ± 0.07	18.1 ± 4.0	10.3 ± 0.6
Pace	133 ± 10	110 ± 6	7 ± 1 (14 ± 2)*	3.8 ± 0.3	29 ± 2	41 ± 5	27 ± 3	25.5 ± 4.6	8.6 ± 1.6	6.4 ± 1.2	196 ± 37	0.63 ± 0.07	17.1 ± 1.6	11.0 ± 1.0
CT B	77 ± 5	104 ± 7	11 ± 2	3.3 ± 0.3	43 ± 4	51 ± 6	28 ± 3	29.6 ± 2.2	8.7 ± 1.1	6.1 ± 0.7	139 ± 14	0.77 ± 0.04	15.6 ± 1.7	11.1 ± 1.1
P (15 min)	67 ± 5	105 ± 5	12 ± 2	3.0 ± 0.3	44 ± 2	56 ± 5	33 ± 4	37.9 ± 1.8	8.9 ± 0.9	5.5 ± 0.6	131 ± 20	0.89 ± 0.14	15.6 ± 2.8	10.9 ± 1.2
P Pace CT	79 ± 4	105 ± 5	11 ± 1	3.2 ± 0.3	41 ± 3	52 ± 5	30 ± 3	33.7 ± 2.0	8.9 ± 0.9	5.8 ± 0.5	155 ± 16	0.71 ± 0.06	16.7 ± 2.6	10.8 ± 1.2
P Pace	128 ± 9	114 ± 4	9 ± 1 (16 ± 2)*	3.2 ± 0.4	25 ± 3	36 ± 5	34 ± 4	27.4 ± 3.7	7.6 ± 0.8	5.5 ± 0.6	212 ± 45	0.62 ± 0.08	17.7 ± 2.8	10.7 ± 0.6
P values														
CT A vs. Pace	<0.001	<0.02	NS	NS	<0.005	<0.01	NS	NS	NS	NS	NS	NS	NS	NS
CT B vs. P	<0.005	NS	NS	NS	NS	NS	NS	<0.05	NS	NS	NS	NS	NS	NS
P vs. P Pace CT	<0.005	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
P vs. P Pace	<0.001	<0.005	NS	NS	<0.001	<0.005	NS	<0.05	NS	NS	NS	NS	NS	NS
Pace vs. P Pace	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
CT B vs. P Pace	<0.001	NS	NS	NS	<0.01	<0.05	NS	NS	NS	NS	NS	<0.05	NS	NS
CT A vs. CT B	NS	NS	NS	NS	NS	<0.05	NS	NS	NS	NS	NS	NS	NS	NS
B. Patients With Coronary Artery Disease														
CT A	77 ± 3	103 ± 4	14 ± 1	3.3 ± 0.1	43 ± 2	51 ± 3	23 ± 3	14.1 ± 3.6	7.4 ± 0.4	6.3 ± 0.4	125 ± 8	0.90 ± 0.09	14.3 ± 1.1	11.5 ± 0.4
Pace	127 ± 3	112 ± 4	11 ± 1 (19 ± 1)*	3.5 ± 0.2	28 ± 1	37 ± 2	23 ± 2	6.5 ± 4.7	7.3 ± 0.5	6.8 ± 0.5	184 ± 16	0.68 ± 0.06	21.3 ± 2.1	11.5 ± 0.4
CT B	78 ± 3	103 ± 4	13 ± 1	3.0 ± 0.1	40 ± 2	47 ± 3	24 ± 2	16.3 ± 4.4	7.7 ± 0.7	6.3 ± 0.6	137 ± 11	0.83 ± 0.07	16.2 ± 1.5	11.6 ± 0.4
P (15 min)	69 ± 2	100 ± 4	15 ± 1	2.6 ± 0.1	38 ± 1	43 ± 2	28 ± 2	22.5 ± 4.6	8.3 ± 0.9	6.2 ± 0.7	133 ± 12	0.86 ± 0.09	15.7 ± 1.9	11.5 ± 0.4
P Pace CT	78 ± 3	105 ± 4	14 ± 1	2.7 ± 0.1	36 ± 2	43 ± 2	28 ± 3	27.3 ± 4.0	8.6 ± 0.7	6.1 ± 0.6	142 ± 16	0.86 ± 0.09	16.0 ± 2.0	11.3 ± 0.3
P Pace	127 ± 3	113 ± 4	12 ± 1 (20 ± 2)*	2.8 ± 0.1	23 ± 1	30 ± 1	30 ± 3	22.2 ± 4.4	8.7 ± 0.7	6.6 ± 0.5	187 ± 15	0.66 ± 0.05	21.2 ± 2.0	11.2 ± 0.4
P values														
CT A vs. Pace	<0.001	<0.001	<0.05	NS	<0.001	<0.001	NS	<0.05	NS	NS	<0.001	<0.005	<0.001	NS
CT B vs. P	<0.001	NS	NS	<0.001	NS	<0.01	<0.001	<0.02	<0.025	NS	NS	NS	NS	NS
P vs. P Pace CT	<0.001	<0.025	NS	<0.005	<0.05	NS	NS	NS	NS	NS	<0.05	NS	NS	NS
P vs. P Pace	<0.001	<0.001	<0.05	<0.05	<0.001	<0.001	NS	NS	NS	NS	<0.001	<0.005	<0.001	NS
Pace vs. P Pace	NS	NS	NS	<0.001	<0.001	<0.001	<0.005	<0.001	<0.005	NS	NS	NS	NS	NS
CT B vs. Pace	<0.001	<0.001	NS	NS	<0.001	<0.001	<0.01	NS	<0.005	NS	<0.001	<0.001	<0.001	NS
CT A vs. CT B	NS	NS	NS	NS	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS

*Figures in parentheses indicate values after temporary interruption of pacing.
†Measurement obtained in three subjects.
Art = arterial; CI = cardiac index; CS = coronary sinus; CSBF = coronary sinus blood flow; CT = control period; CVR = coronary vascular resistance; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; MVO_2 = myocardial oxygen consumption; NS = not significant; P = propranolol; *P* = probability; Pace = atrial pacing; SI = stroke index; TPR = total peripheral resistance.

TABLE III

Summary of Data in Nine Patients With and Six Patients Without Improvement After Propranolol Therapy

	Heart Rate (beats/min)		LVEDP (mm Hg)		Lactate (% extraction)		CSBF (ml/min)		CVR (units)		MVO_2 (ml/min)		(Art-CS) O_2 (ml/100 ml)	
	With	Without	With	Without	With	Without	With	Without	With	Without	With	Without	With	Without
CT A	79 ± 3	78 ± 5	13 ± 1	13 ± 2	18.1 ± 4.1	6.6 ± 6.0	126 ± 15	131 ± 10	0.96 ± 0.15	0.74 ± 0.04	13.0 ± 1.5	16.4 ± 1.9	10.7 ± 0.4	12.4 ± 0.6
Pace	135 ± 5	120 ± 6	11 ± 2 (18 ± 1)*	13 ± 1 (21 ± 2)*	14.4 ± 6.5	−10.7 ± 4.9	200 ± 31	191 ± 19	0.71 ± 0.11	0.60 ± 0.07	22.2 ± 3.6	24.4 ± 3.2	11.2 ± 0.3	12.7 ± 0.7
CT B	78 ± 3	80 ± 7	12 ± 1	13 ± 2	24.1 ± 5.6	2.2 ± 5.0	148 ± 21	137 ± 11	0.86 ± 0.13	0.77 ± 0.06	17.6 ± 2.9	16.8 ± 2.0	11.6 ± 0.6	12.2 ± 0.5
P	69 ± 3	70 ± 6	14 ± 1	15 ± 2	28.4 ± 6.8	10.6 ± 7.6	140 ± 19	140 ± 22	0.85 ± 0.11	0.80 ± 0.10	16.4 ± 3.3	17.1 ± 3.4	11.4 ± 0.6	11.9 ± 0.7
P-Pace CT	79 ± 4	79 ± 6	14 ± 1	15 ± 2	32.4 ± 4.8	13.4 ± 7.3	134 ± 16	172 ± 40	0.96 ± 0.16	0.72 ± 0.10	14.7 ± 1.9	20.3 ± 4.9	11.4 ± 0.5	11.8 ± 0.4
P Pace	133 ± 5	121 ± 6	9 ± 2 (18 ± 1)*	17 ± 2 (25 ± 2)*	26.7 ± 5.3	7.8 ± 7.2	190 ± 28	197 ± 25	0.68 ± 0.08	0.61 ± 0.05	20.4 ± 3.1	25.2 ± 3.9	10.8 ± 0.5	12.7 ± 0.3
P values														
CT A vs. Pace	<0.001	<0.005	NS	NS	NS	<0.05	<0.025	<0.02	<0.05	NS	<0.001	<0.01	NS	NS
CT B vs. P	<0.005	<0.02	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
P vs. P Pace	<0.001	<0.001	<0.02	NS	NS	NS	<0.01	<0.01	<0.01	<0.05	<0.02	<0.01	NS	NS
Pace vs. P Pace	NS	<0.025	NS	NS	<0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS
CT A vs. CT B	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	<0.05	NS	NS	NS

*Figures in parentheses indicate values after temporary interruption of pacing.

Art-CS = arterial-coronary sinus; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; LVEDP = left ventricular end-diastolic pressure; MVO_2 = myocardial oxygen consumption; NS = not significant; *P* = probability.

diastolic pressure (mm Hg), TPR = total peripheral resistance (units), CO = cardiac output in liters/min, CVR = coronary vascular resistance (units), CSBF = coronary sinus blood flow (ml/min) and MVO_2 = myocardial oxygen consumption (ml/100 ml).

Plasma lactate determinations were carried out with an automated fluorometric method and expressed in mg/100 ml.[9] In our hands, this method has a coefficient of variation of 4 percent for 50 determinations. Blood was collected in heparinized tubes, centrifuged immediately at 3° C and the plasma frozen at −30° C until analysis. Percent lactate extraction was calculated as the ratio of arteriovenous difference to the arterial level (A −V)/A × 100.

Statistical analysis was performed using Student's *t* test with paired and unpaired comparisons where appropriate.

Results

The hemodynamic, coronary sinus blood flow and myocardial metabolic data for the normal group and for the patients with coronary disease are shown in Table II. In instances where mean values in a table represent less than the mean value of the total sample number, there were sampling difficulties that precluded the acquisition of enough blood for metabolic analysis. In the following discussion of the results any direct reference to numerical changes implies a statistically significant change.

Normal subjects (Table IIA): The response to atrial pacing in the six normal subjects was characterized by an increase in mean arterial pressure (102 to 110 mm Hg) and decreases in left ventricular end-diastolic pressure (12 to 7 mm Hg), stroke index (48 to 29 ml/beat per m^2 and left ventricular stroke work index (60 to 41 g-m/m^2). There was no change in lactate extraction or myocardial oxygen consumption and, although coronary sinus blood flow increased, the change was not statistically significant. Propranolol produced a decrease in heart rate (77 to 67 beats/min) and an increase in lactate extraction (29.6 to 37.9 percent) but no other significant changes. Restoration of the heart rate to levels present during Control B did not produce any significant changes. The response to atrial pacing after propranolol in this normal group failed to demonstrate any significant difference in the pattern of hemodynamics, myocardial oxygen consumption, coronary sinus blood flow or lactate extraction from that seen in the original pacing period.

Patients with coronary artery disease (Table IIB): Atrial pacing in this group of 19 patients produced an increase in mean arterial pressure (103 to 112 mm Hg) and a decrease in left ventricular end-diastolic pressure (14 to 11 mm Hg) followed by an increase to 19 mm Hg after interruption in pacing. Stroke index decreased from 43 to 28 ml/beat per m^2, left ventricular stroke work index from 51 to 37 g-m/m^2 and lactate extraction from 14.1 to 6.5 percent. Myocardial oxygen consumption increased from 14.3 to 21.3 ml/min and coronary sinus blood flow from 125 to 184 ml/min. No change was observed in arteriovenous oxygen difference. In this group propranolol reduced heart rate (78 to 69 beats/min), left ventricular stroke work index (47 to 43 g-m/m^2) and cardiac index (3.0 to 2.6 liters/min per m^2)

and increased total peripheral resistance (24 to 28 units) and lactate extraction (16.3 to 22.5 percent) but produced no change in myocardial oxygen consumption or coronary sinus blood flow. Restoration of heart rate to control levels after propranolol increased mean arterial pressure (100 to 105 mm Hg) and cardiac index (2.6 to 2.7 liters/min per m^2) and coronary sinus blood flow (133 to 142 ml/min). A comparison of data during pacing after propranolol versus data obtained during the initial pacing period revealed significant differences in left ventricular stroke work index (30 versus 37 g-m/m^2), stroke index (23 versus 28 ml/beat per m^2), cardiac index (2.8 versus 3.5 liters/min per m^2), total peripheral resistance (30 versus 23 units), arterial lactate (8.7 versus 7.3 mg/100 ml) and lactate extraction (22.2 versus 6.5 percent) but similar values for left ventricular end-diastolic pressure (both during and after interruption of pacing), arteriovenous oxygen difference, myocardial oxygen consumption and coronary sinus blood flow.

Clinical response (Table III): Analysis of the clinical response of the 19 patients with coronary artery disease revealed that angina developed in 15 during the first pacing period. The magnitude of the pacing stress was similar in these 15 patients and in the 4 who did not experience angina. However, pacing was limited in the latter group because of A-V block during the initial pacing period. Of the 15 who had angina, 9 showed clinical improvement in the second pacing period after propranolol and 6 did not. Table III shows the changes in heart rate, left ventricular end-diastolic pressure, coronary sinus blood flow, myocardial oxygen consumption, arterial and coronary sinus lactate and lactate extraction in the groups with and without improvement. The group with improvement had a normal lactate extraction at rest with minimal change during pacing. Pacing after propranolol was associated with a significantly greater level of arterial lactate and of lactate extraction than during the initial pacing period. The group without improvement showed frank lactate production during the first pacing period; during pacing after propranolol this group manifested lactate extraction, but the level was not statistically different from that of the original pacing period.

The changes in coronary sinus blood flow in the groups with and without improvement were similar in response to pacing and no change was seen in either group in response to propranolol. Restoration of heart rate after propranolol was met with an increase in coronary sinus blood flow in the group without improvement (from 140 to 172 ml/min). However, during pacing after propranolol, a response similar to that of the initial pacing period was seen in both groups. The response of myocardial oxygen consumption to pacing before and after propranolol was also similar in the two groups. In the group with improvement the S-T segment depression during the initial pacing period was 1.2 ± 0.3 mm and after propranolol this decreased to 0.1 ± 0.1 mm ($P < 0.01$). In the group without improvement, the S-T segment depression was 1.4 ± 0.7 mm during the initial pacing period and 1.5 ± 0.7 mm after propranolol.

In the five simulated studies, during the first pacing period three patients had angina that was reproducible during the second pacing period. Similar hemodynamic, coronary sinus blood flow and electrocardiographic changes occurred throughout both pacing periods. No significant change was seen in arterial lactate concentration or lactate extraction but arterial glucose (mg/100 ml) increased as follows: 102.8 ± 6.7 (Control A), 119.0 ± 6.1 (Pace), 122.4 ± 8.3 (Control B), 119.2 ± 10.7 (Propranolol simulation) and 129.4 ± 11.2 (Propranolol-Pace simulation).

Discussion

Propranolol is widely used in the therapy of angina pectoris. Its therapeutic benefit is derived from the sum of a series of actions at different sites in the cardiovascular system.[1] Hence, the negative inotropic and chronotropic effects may be partly offset by the tendency to increase left ventricular volume and wall tension.

Before we discuss the changes attributable to propranolol, some comment regarding the diazepam premedication in this study may be warranted. It is known that intravenously administered diazepam may reduce arterial pressure, left ventricular end-diastolic pressure and myocardial oxygen consumption in normal subjects and patients with coronary artery disease.[10] In this study the modest oral dose given at least 2 hours before the first set of control measurements probably had little or no influence on dynamics at that time since the drug is rapidly absorbed, reaching peak plasma levels in 1 hour, and has a short half-life of 2 to 3 hours.[11] This view is reinforced by the comparability of the measurements made during control periods A and B.

Effects of propranolol: Our study demonstrates that propranolol can favorably influence the anginal threshold as assessed with atrial pacing; 9 of the 15 patients who had angina during the initial pacing period showed clinical improvement. Although propranolol produced a decrease in heart rate, cardiac index and stroke work, these changes were not accompanied by a change in coronary sinus blood flow or myocardial oxygen consumption. However, there was a consistent increase in the extraction of lactate by the heart in these subjects and a diminution in the electrocardiographic manifestations of ischemia.

When heart rate was restored to control levels and the negative chronotropic effect thereby removed, mean arterial pressure, cardiac index and coronary sinus blood flow increased slightly and no change was seen in myocardial oxygen consumption or lactate metabolism. Thus, the negative chronotropic effect did not contribute to an overall decrease in myocardial oxygen consumption and did not affect lactate metabolism.

The influence of propranolol on the hemodynamic response to atrial pacing in these patients was characterized by a significant reduction of cardiac index, stroke index and left ventricular filling pressures. The reduction in cardiac index without an associated change in filling pressure or arterial pressure or heart rate was presumably secondary to the direct negative inotropic

effect of propranolol and was approximately 20 percent.

Comparison of patients with and without improvement: A comparison of the nine patients who showed improvement with the six who did not show improvement after propranolol therapy yields some interesting differences. In part, the differences in response may reflect more advanced coronary artery disease in the group without improvement, as evidenced by the lower pacing rate required to achieve angina and the abnormal resting lactate metabolism (6.6 percent). The larger increment in coronary sinus blood flow in this group seen when heart rate was restored to control levels after propranolol therapy may partly reflect the smaller overall increment in rate required to produce angina in this group but is otherwise unexplained. Of interest also was that left ventricular end-diastolic pressure decreased during pacing after propranolol in the group with improvement and increased in the group without improvement; however, there was no change in the post-pacing left ventricular end-diastolic pressure in the former group. Previous studies with both nitroglycerin and phlebotomy have shown that reduction in pacing-induced angina is associated with reduction in the post-pacing left ventricular end-diasolic pressure.[12,13] The difference in the response of the post-pacing left ventricular end-diastolic pressure with propranolol is presumed to be related to this drug's different mechanisms of action and mode of relief of pacing-induced angina. Despite this change in clinical and hemodynamic data after propranolol, lactate metabolism in the group without improvement showed a shift from production to extraction during pacing that, although not statistically significant, was of similar magnitude to the change seen in the group with improvement.

The protection propranolol provides against pacing-induced angina may not be representative of its effects on exercise-induced angina. Much of the protective effect in the latter situation may be mediated by a blunting of the increase in heart rate and circulating catecholamines that accompanies muscular exercise.

Effect of propranolol on coronary hemodynamics: Little information exists concerning the influence of propranolol on coronary hemodynamics, myocardial oxygen consumption and lactate metabolism. Wolfson and Gorlin[4] found that propranolol produced a significant reduction in coronary flow as measured with the krypton technique. Their 20 patients also had a decrease in myocardial arteriovenous oxygen difference and coronary vascular resistance, thus suggesting the possibility of overall coronary vasoconstriction. However, when the individual data in their 12 patients with coronary disease are analyzed with use of a paired *t* test the changes in myocardial oxygen consumption and arteriovenous oxygen difference are shown to be not significant, a finding in keeping with our data.

Propranolol and myocardial oxygen consumption: The absence of a significant reduction in myocardial oxygen consumption at rest and during the pacing stress after administration of propranolol may be a reflection of (1) regional redistribution of coronary flow that occurred but was not measured by the calculation of coronary sinus blood flow[14]; or (2) increased ventricular wall tension that counterbalanced factors leading to a decrease in myocardial oxygen consumption. An increase in wall tension could have been mediated in part by the increased peripheral resistance and by an increase in ventricular volume. Although left ventricular filling pressure did not increase after administration of propranolol, this drug can increase volume secondary to an increase in ventricular compliance.[15]

Propranolol and lactate metabolism: The effects of propranolol on increasing lactate extraction in both the normal subjects and the patients with coronary artery disease merits further comment. Because this change occurred without significant alteration in coronary sinus blood flow or myocardial oxygen consumption, it possibly reflects a primary metabolic effect exerting its influence either directly on the myocardium or on peripheral sites. Propranolol blocks the increase in myocardial free fatty acid uptake induced by atrial pacing and the intracoronary infusion of catecholamines in the dog.[16] It also blocks the release of free fatty acids from the adipose depots, causing a reduction in arterial levels in man, thereby favoring a preferential shift to metabolism of other substrates such as lactate.[17] In eight patients studied by Lewis et al.,[18] there was no overall change in myocardial lactate extraction after a 10 mg infusion of propranolol although three patients showed an increase in lactate metabolism and five a decrease. Wolfson and Gorlin[4] studied lactate metabolism in eight patients after an intravenous infusion of 5 mg of propranolol; although no change was observed, they noted in six of the eight-paired arterial and coronary sinus samples a shift toward an increase in lactate extraction.

Mueller et al.[5] studied the hemodynamic and metabolic effects of intravenously administered propranolol (0.1 mg/kg) in 20 patients with acute myocardial infarction who were free of left ventricular failure. Propranolol produced a 17 percent decrease in coronary blood flow and a 22 percent reduction in myocardial oxygen consumption with an 86 percent increase in myocardial lactate extraction. This was achieved without a significant decrease in the extraction of free fatty acid. Although their data provide some evidence that increased lactate extraction may be secondary to a primary hemodynamic effect, comparison with our data is difficult because of the different nature of the patient population. It should also be noted that arterial lactate increased in our patients who showed improvement, and this finding may in part account for the increase in lactate extraction. However, a trend toward increased extraction was seen in the group without improvement although arterial lactate was unchanged. The reason for the increase in arterial lactate is unclear, but the simulated studies suggest that it is not related to the intermittent carbohydrate infusions involved in the coronary flow determinations although these latter studies demonstrate an elevation in the blood glucose

level during the course of the investigation. This elevation was of modest proportion and did not affect the reproducibility of the clinical, hemodynamic or electrocardiographic changes evident in this group.

In conclusion, our study demonstrates that in some patients with coronary artery disease propranolol administered as an intravenous bolus injection is capable of modifying the anginal threshold as assessed with atrial pacing. The negative chronotropic effect of propranolol has little influence on coronary or systemic hemodynamics. The clinical response appears to be independent of global changes in coronary sinus blood flow and myocardial oxygen consumption.

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Prolonged Salutary Effects of Isosorbide Dinitrate and Nitroglycerin Ointment on Regional Left Ventricular Function

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To assess the long-term effects of orally and topically administered nitrates on left ventricular function, 11 patients with previous myocardial infarction were studied with use of isosorbide dinitrate, 20 mg orally, nitroglycerin ointment, 12.5 to 40 mg and placebo ointment. Both nitrates produced a sustained decrease in systolic blood pressure and estimated left ventricular wall stress but no change in heart rate during 4 hours of study. The triple product of heart rate, systolic blood pressure and left ventricular ejection time decreased by 21 percent after administration of isosorbide dinitrate ($P < 0.001$) and 19 percent after administration of nitroglycerin ointment ($P < 0.001$). The echocardiographic left ventricular end-diastolic dimension decreased significantly after isosorbide dinitrate (from 52.4 to 49.2 mm at 2 hours, $P < 0.01$) and nitroglycerin ointment (from 52.4 to 50.5 mm, $P < 0.01$). The end-systolic dimension was similarly reduced. Left ventricular sites showing abnormally small excursion (less than 3 mm) on wall motion videotracking showed improved motion after the administration of each nitrate, and the velocity of systolic inward motion was consistently increased after each. Thus, determinants of myocardial oxygen consumption, such as systolic blood pressure, left ventricular ejection time, left ventricular size and triple product appear to be consistently reduced for at least 4 hours after administration of isosorbide dinitrate and nitroglycerin ointment, and impairment of left ventricular wall motion appears to be significantly decreased.

The circulatory effects of sublingually administered nitroglycerin have been well delineated.[1–3] Recently, the effects of nitroglycerin on left ventricular segmental wall motion have been studied in the conscious dog with use of implanted miniature ultrasonic crystals,[4] and in man with use of noninvasive wall motion videotracking.[5]

Although most observers have reported an improvement in left ventricular segmental wall motion after sublingual administration of nitroglycerin,[4–13] no data have been available concerning the long-term effects of orally or topically administered nitrates on the dimensions or wall motion of the left ventricle in patients with ischemic heart disease. The marginally ischemic segments of the chamber might be expected to show a functional improvement after the administration of long-acting nitrates, similar to that occurring transiently after sublingual administration of nitroglycerin. Such prolonged beneficial effects might also have therapeutic implications for patients with acute or chronic heart failure associated with left ventricular segmental wall motion abnormalities.

The purpose of this study was to define the effects of two long-acting nitrates, isosorbide dinitrate and nitroglycerin ointment, on left ventricular dimensions as assessed with echocardiography, on regional left ventricular function as studied with wall motion videotracking and on several determinants of myocardial oxygen consumption including systolic blood pressure, left ventricular ejection time and heart rate. In

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addition, the hemodynamic effects of the two nitrates and their duration of action were compared.

Patients and Methods

Patients: Eleven patients, nine men and two women with a mean age of 53.1 years (range 35 to 69 years) were selected for the study. All patients had had a transmural myocardial infarction 7 to 66 months (mean 22.2 months) previously. The diagnosis of myocardial infarction was made in the Myocardial Infarction Research Unit of the University Hospital, San Diego, on the basis of the following criteria: (1) a history of typical prolonged chest pain, (2) electrocardiographic changes showing the evolution of a pattern of transmural infarction, and (3) characteristic elevation of serum enzyme levels (creatine kinase, glutamic oxaloacetic transaminase, lactic dehydrogenase). In four patients the location of the infarct was anterior, in six inferior and in one lateral. All patients had used nitroglycerin sublingually with benefit for the relief of angina pectoris and five patients had had angina within 1 month of the study. No patient was taking long-acting nitrates. One patient had a history of labile hypertension. None had overt heart failure.

Wall motion videotracking: This was performed with our previously described method[14] using a commercially available videotracking device (Biotronix Heart Motion Videotracker) interfaced with a 23 cm image intensifier. The fluoroscopic cardiac silhouette was displayed on a Plumbicon television system, and left ventricular wall motion was recorded on a Honeywell Visicorder photographic system with a simultaneous electrocardiographic lead II and a phonographic tracing of the heart sounds. Recordings were made from four sites on the left ventricular silhouette in the frontal, 10° right anterior oblique and 10° left anterior oblique projections. Site 1 was the highest segment showing left ventricular systolic inward movement and site 4 was the apical portion of the left ventricular silhouette. The ventricular border between sites 1 and 4 was divided equally into a higher (site 2) and a lower (site 3) segment. To assure reproducibility of the tracked sites during the drug studies, the relation of each site to the ribs was carefully recorded. Thus, the same sites were compared in a paired fashion during the control state and during drug effect. Each study was performed with the patient in the supine position during maximal inspiration; special care was taken to avoid any Valsalva effects.

The amplitude and the peak velocity of systolic inward motion were measured during three consecutive cardiac cycles from each recorded site in the three projections. These values were corrected using a known recorded calibration. Correction was also made for magnification, using the distance between the patient (mid chest) and the X-ray tube. The mean values for the amplitude and the maximal velocity of systolic inward movement were then determined for each site from the three projections. Inward motion was measured from the end-diastolic reference point (peak of QRS complex). Abnormal wall motion was also analyzed qualitatively as described previously[5] using a modification of the classification of Herman and Gorlin.[15] The movement of the recorded sites was described as normal contraction, hypokinesia, akinesia, asynchrony or dyskinesia. With use of the lowest measured values for excursion and velocity of motion of 60 left ventricular sites in 10 subjects with normal coronary angiograms and no clinical evidence of heart disease, the lower limit of normal systolic excursion was defined as 3.0 mm and the normal velocity of systolic inward excursion as 20 mm/sec. When these 10 normal subjects were studied on two separate occasions, results were reproducible, and no significant difference was found in the movement of sites at different locations on the left ventricular border.

Hypokinesia was defined as a systolic excursion of less than 3.0 mm, *asynchrony* as early systolic outward movement followed by hypokinetic or normal systolic motion, *akinesia* as the absence of systolic motion and *dyskinesia* as a systolic outward bulging. A site with abnormal wall motion was considered to respond favorably to the nitrate if its motion either became normal or was reduced in severity (for example, akinesia became hypokinesia or dyskinesia became asynchrony). Only sites without dyskinesia in the control state were included in the quantitative analysis of the extent and velocity of contraction.

Echocardiograms: These were recorded using a Picker Echoview X instrument and a 2.25 or 1.6 megahertz transducer with a diameter of 0.5 and 0.75 inches (1.27 and 1.91 cm), respectively, and beam collimation with a depth of 5 and 10 cm. The repetition rate of the transducers was 1,000/sec. The same transducer was used serially in all studies in the same patient. An indirect carotid pulse tracing and electrocardiographic lead II were recorded simultaneously with the M mode echocardiograms at a paper speed of 100 mm/sec using a Honeywell 1856 strip-chart recorder.

All patients were studied in the left lateral decubitus position (approximately 45°) during normal respiration. The transducer was positioned close to the left sternal border in the second, third, fourth and fifth intercostal spaces sequentially and the ultrasonic beam was directed posteriorly and slightly medially until the echogram of the anterior leaflet of the mitral valve was identified. The transducer was then directed inferolaterally until the echoes from the endocardial surface of the interventricular septum and the posterior left ventricular wall could be clearly identified. With careful adjustment of the gain and depth controls a clear image of the echoes could be obtained. Recordings of the left ventricular dimension were made at an angle just below the anterior leaflet of the mitral valve and showed fragmental echoes of the valve.[16]

After the first study in each patient, the transducer site on the chest was recorded to assure identical orientation in subsequent studies. Great care was also taken to reproduce identical recordings in relation to the mitral apparatus. All the patients showed a qualitatively normal septal and posterior wall motion. The control echocardiographic and videotracking recordings were performed in the left lateral and supine position, respectively, after the blood pressure and heart rate had remained stable for at least 30 minutes. Before any measurements were made from the recorded tracings all the echocardiograms and videotracking studies were pooled and randomized.

The left ventricular dimension was measured at end-diastole at the peak of the QRS complex (EDD) and at end-systole (ESD), which was taken as the minimal distance between the left ventricular septal and posterior wall endocardium during systole. The thickness of the septal and posterior left ventricular walls was also measured at end-diastole, end-systole and before inscription of the P wave. The left ventricular ejection time (LVET) was measured from the steep upstroke of the carotid pulse tracing to the dicrotic notch. The left ventricular ejection time was also corrected for heart rate and expressed as the left ventricular ejection time index (LVETI) as described by Weissler et al.[17]

The percent internal dimension shortening (%Δ) of the left ventricle was calculated as: $(EDD - ESD)/EDD \times 100$.

The mean rate of internal dimension shortening (Vcf) was calculated as $(EDD - ESD)/(EDD \times LVET)$.

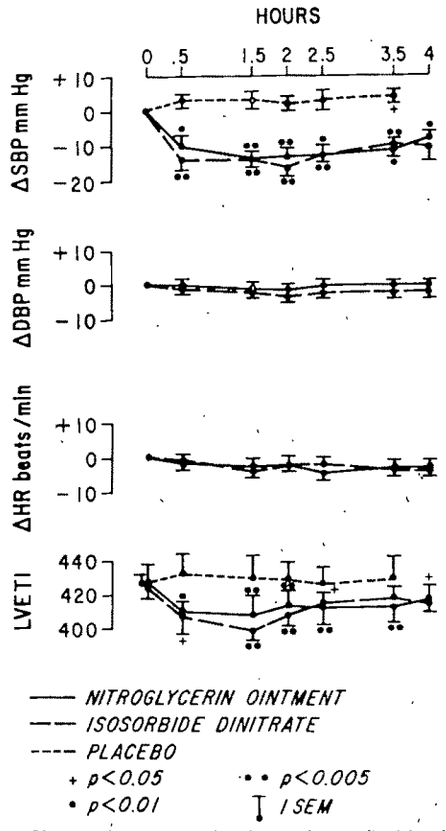


FIGURE 1. Change from control values of systolic blood pressure (ΔSBP), diastolic blood pressure (ΔDBP) and heart rate (ΔHR) after the administration of isosorbide dinitrate, nitroglycerin ointment and placebo ointment. The lowest panel shows the left ventricular ejection time index (LVETI) plotted against time. The probability (p) values refer to the comparison with control values. SEM = standard error of the mean.

The mid systolic wall stress (σ) was estimated as[18]:

$$\sigma = \frac{1 + b^3/2r^3}{b^3 - a^3} Pa^3 \times 1.36$$

where P is the systolic blood pressure in mm Hg, a represents half the internal left ventricular dimension in mid systole and b represents the external radius of the chamber, which is calculated as: a + the mean wall thickness in mid systole. Mid systole was timed from the indirect carotid pulse as left ventricular ejection time divided by 2. The left ventricular stress was calculated at mid wall substituting (a + b)/2 for r. The constant (1.36) is the conversion factor to g/cm^2.

Systemic arterial blood pressure was obtained by cuff sphygmomanometer and monitored with the heart rate at 5 to 10 minute intervals throughout the study period.

Protocol: At the time of the study, the patients were fasting, except for a light liquid breakfast. The preparations tested were 2 percent nitroglycerin ointment (Nitrobid®),* isosorbide dinitrate (Sorbitrate®), 20 mg given orally and a placebo consisting of inert ointment base. The ointment was applied to the right pectoral region over an area of approximately 54 cm^2, covered with a wrap commercially supplied for this purpose and sealed with tape. The effective dose of nitroglycerin ointment was individually determined for each patient, starting with 12.5 mg (1 inch [2.5 cm]). If the initial dose did not produce a reduction in systolic blood pressure of at least 10 mm Hg 30 minutes after the application with the patient in a sitting position, the dose was increased by 1 inch until this hemodynamic effect was observed. Eight patients responded to the first dose, one patient required a total of 25 mg and another a total of 40 mg. All subsequent measurements were made with the patient supine. All 11 patients received orally 20 mg of isosorbide dinitrate, which produced a reduction in systolic blood pressure of at least 10 mm Hg in each. Seven patients had a placebo study using 1 inch of inert paste. The order of administration of the preparations was decided randomly. There was an interval of 2 to 15 days between serial studies in each patient. The patients were told that each preparation was different but were not told that one was pharmacologically inert. Mild headache developed in eight patients after the administration of nitroglycerin ointment and in seven patients after isosorbide dinitrate.

The echocardiographic studies were repeated at 30, 90, 120, 150, 210 and 240 minutes and the videotracking recordings at 1 and 3 hours after administration of the drugs, using the time of the last effective dose of nitroglycerin ointment as a reference.

Statistical analyses were made with Student's *t* test, using Dunnett's method for nonindependent tests.[19]

* This drug and the inert ointment were kindly supplied by Marion Laboratories, Inc.

TABLE I

Qualitative Analysis of Segmental Wall Motion

	Isosorbide Dinitrate (44 sites in 11 patients)			Nitroglycerin Ointment (40 sites in 10 patients)		
	Control	1 Hour	3 Hours	Control	1 Hour	3 Hours
Normal sites	19	25	26	15	21	22
Hypokinesia	10	3	4	7	4	6
Asynchrony	8	11	8	11	10	8
Akinesia	3	2	3	2	2	1
Dyskinesia	4	3	3	5	3	3

Results

Heart rate, arterial blood pressure and left ventricular ejection time index: In contrast to placebo, both isosorbide dinitrate and nitroglycerin ointment produced a significant decrease in systolic blood pressure that began by 30 minutes and persisted for 3.5 and 4 hours, respectively (Fig. 1). After administration of isosorbide dinitrate, the maximal effect was found at 2 hours (decrease from 126 ± 4 [standard error of the mean] to 110 ± 4 mm Hg, $P < 0.005$) and the corresponding effect of nitroglycerin ointment at 120 minutes was to reduce the blood pressure from 118 ± 4 to 105 ± 3 mm Hg ($P < 0.005$). None of the three preparations produced any significant changes in heart rate or diastolic blood pressure although both variables tended to be slightly decreased (Fig. 1). Left ventricular ejection time index decreased significantly after both isosorbide dinitrate (from 424 ± 7 to 408 ± 10 by 30 minutes, $P < 0.05$) and after nitroglycerin ointment (from 428 ± 10 to 412 ± 7 by 30 minutes, $P < 0.01$), significant effects lasting for 2.5 and 4 hours, respectively (Fig. 1).

The triple product (heart rate × systolic blood pressure × left ventricular ejection time) was reduced after administration of isosorbide dinitrate from 2.56

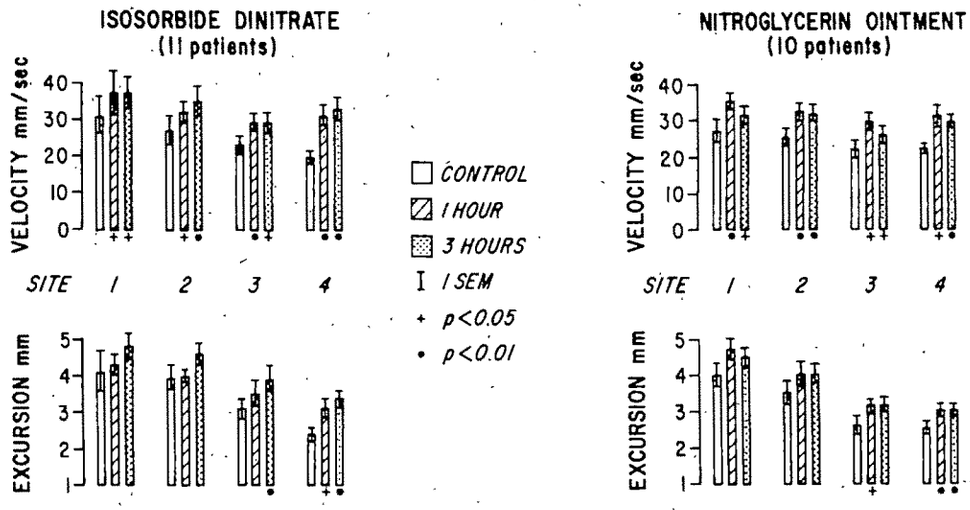


FIGURE 2. The excursion and velocity of systolic inward motion at sites 1 (high left ventricle) to 4 (apex) on the left ventricular silhouette, during the control period and 1 and 3 hours after the administration of isosorbide dinitrate and nitroglycerin ointment. Probability (p) values indicate the comparison with control values. SEM = standard error of the mean.

$\times 10^3$ to 2.02×10^3 ($P < 0.001$) by 1.5 hours and was still reduced (to 2.25×10^3) at 4 hours ($P < 0.01$). After nitroglycerin ointment, the triple product decreased from 2.47×10^3 to 2.0×10^3 ($P < 0.001$) at 1.5 hours and to 2.16×10^3 at 4 hours ($P < 0.05$). No significant changes in left ventricular ejection time index or triple product were seen after placebo.

Left ventricular wall motion: In the study of segmental wall motion with videotracking the functional characteristics of four sites on the left ventricular silhouette were evaluated qualitatively and quantitatively.

The qualitative changes in segmental wall motion are shown in Table I. The different number of sites in each group before the administration of the two nitrates is explained by the difference in total number of sites (11 versus 10 patients) and partly by four sites in two patients showing different contraction patterns on the two occasions. Three sites manifested hypokinesia before administration of isosorbide dinitrate but asynchrony before nitroglycerin and one site showing akinesia before isosorbide dinitrate showed dyskinesia before nitroglycerin. The other 36 sites were identically classified in the two control periods.

Before the administration of isosorbide dinitrate, 19 sites (43 percent) showed normal contraction, whereas 25 sites (57 percent) were normal 1 hour and 26 (59 percent) 3 hours after drug administration. A total of

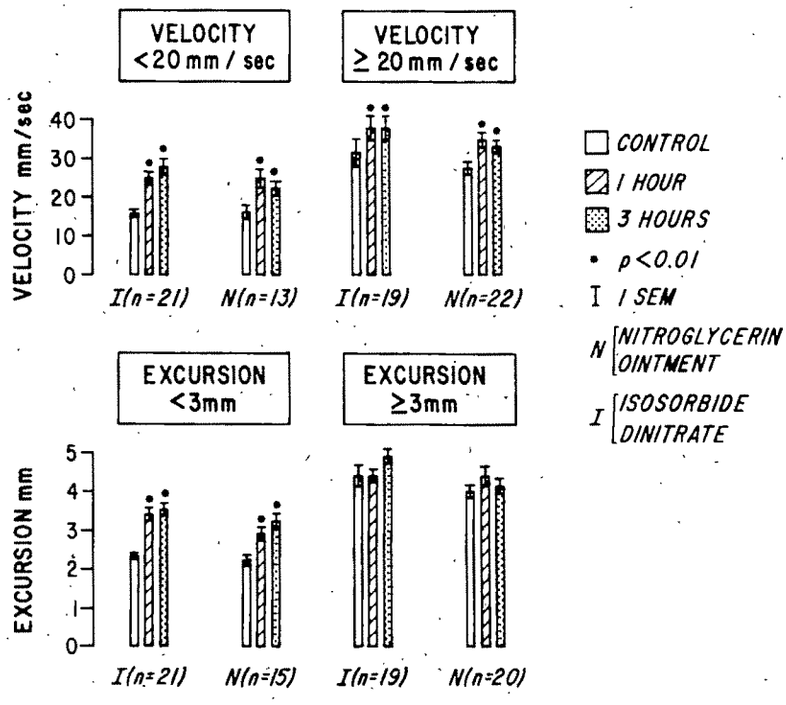


FIGURE 3. The excursion and velocity of systolic inward motion in sites showing an excursion at rest of less than 3 and of 3 or more mm and a velocity at rest of less than 20 and 20 or more mm/sec. Probability (p) values refer to comparison with control values. SEM = standard error of the mean.

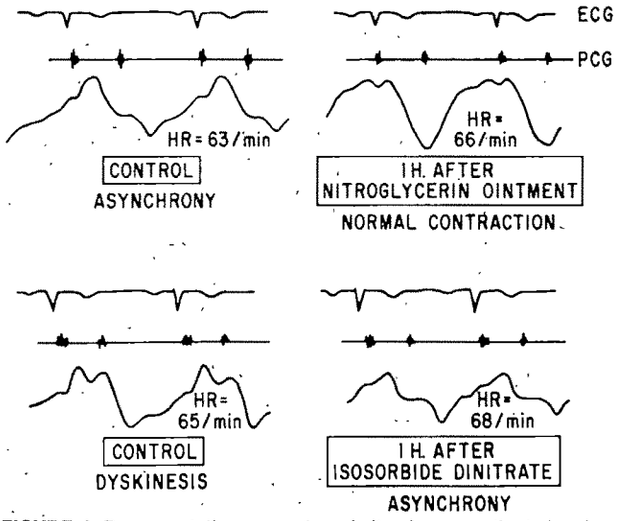


FIGURE 4. Representative examples of sites in one patient showing a qualitative change in contraction 1 hour (H.) after the administration of nitroglycerin ointment **(upper panel)** and isosorbide dinitrate **(lower panel)**. The **upper panel** shows a site changing from asynchrony to normal contraction and the **lower panel** a site changing from dyskinesia to asynchrony. ECG = electrocardiogram; HR = heart rate; PCG = phonocardiogram.

9 sites (20 percent) showed qualitative improvement of contraction at 1 hour and 12 sites (27 percent) at 3 hours. After nitroglycerin ointment, the number of normal sites increased from 15 (38 percent) to 21 (53 percent) at 1 hour and to 22 (55 percent) at 3 hours. As with isosorbide dinitrate, 9 and 12 sites showed qualitative improvement at 1 and 3 hours, respectively, after application of the ointment. No qualitative changes were found in segmental wall motion after placebo.

Quantitative analysis of improvement indicated that placebo produced no significant changes in the mean excursion (3.6 ± 0.3 mm before placebo, 3.5 ± 0.3 mm 3 hours after placebo) or velocity of systolic inward motion (25 ± 2 mm/sec before placebo and 24 ± 2 mm/sec at 3 hours) of the 26 left ventricular sites without dyskinesia. The quantitative analysis of the extent and velocity of contraction of these sites without dyskinesia before and after the two nitrates is shown in Figures 2 and 3. Significant improvement in the systolic inward motion was found at sites 3 (no. = 10) and 4 (no. = 8) 3 hours after isosorbide dinitrate. The inward excursion at site 3 increased from 3.0 ± 0.3 to 3.9 ± 0.4 mm (P <0.01) and at site 4 from 2.4 ± 0.2 to 3.4 ± 0.2 mm (P <0.005). The excursion of sites 3 (no. = 8) and 4 (no. = 7) was also significantly improved after nitroglycerin ointment—in site 3 from 2.6 ± 0.3 to 3.1 ± 0.2 mm by 1 hour (P < 0.05) and in site 4 from 2.4 ± 0.2 to 3.0 ± 0.3 mm by 3 hours (P <0.01). The velocity of systolic inward motion was consistently improved after each nitrate in the upper sites (1 and 2) as well as in the lower sites (3 and 4) by 1 and 3 hours (Fig. 2).

Similarly, the motion of the sites showing an excursion of less than 3 mm during the control period improved significantly after both isosorbide dinitrate (2.4 ± 0.2 to 3.5 ± 0.2 mm at 3 hours, no. = 21) (P <0.001) and nitroglycerin ointment (2.2 ± 0.2 to 3.2 ± 0.2 mm at 3 hours, no. = 15) (P <0.001), whereas sites with normal excursion at rest showed no further increase in excursion (Fig. 3). By contrast, the velocity of systolic inward motion in all sites was consistently increased after each nitrate.

Figure 4 shows a representative example of asynchrony changing to normal wall motion 1 hour after nitroglycerin ointment at one site and dyskinesia changing to asynchrony at another site in the same patient 1 hour after isosorbide dinitrate.

Echocardiographic findings (Table II): Thirty minutes after the administration of isosorbide dinitrate the end-diastolic dimension decreased from 52.4 ± 2.7 to 50.2 ± 2.7 mm (P <0.01) and remained significantly reduced for 3.5 hours (51.1 ± 2.8 mm) (P <0.01). Nitroglycerin ointment produced similar changes in the end-diastolic dimension, from a control value of 52.6 ± 2.3 to 50.2 ± 2.5 mm (P <0.01) at 30 minutes and 51.0 ± 2.6 mm at 4 hours (P <0.01). Consistent reductions of a similar degree were found in the end-systolic dimension after isosorbide dinitrate, lasting 3.5 hours, and after nitroglycerin ointment, lasting 4 hours. The difference between the end-diastolic and end-systolic dimensions was not significantly altered by any of the three preparations. The reduction in left ventricular dimensions was accompanied by an increase in septal and posterior wall thickness in end-diastole and end-systole after each nitrate (Table II). However, these changes were of smaller magnitude than the dimensional changes. None of the increases in wall thickness persisted for more than 3.5 hours. No significant changes were found in left ventricular dimension or wall thickness after placebo (Table II).

To obtain a measure of the reproducibility of the serial echocardiographic measurements in the same patients, the mean absolute difference between serial individual values in the group receiving placebo was computed and also expressed as a percent of the control values before placebo (Table II). There was a range of mean absolute differences from 0.4 to 0.9 mm for measurements of left ventricular dimension and wall thickness (1.1 to 4.8 percent of the respective control values). Some of this variability may represent small but real changes in the echocardiographic measures.

Although the percent internal dimension shortening tended to increase after administration of isosorbide dinitrate and nitroglycerin ointment, these changes were small and only significant early after administration. However, because of the decrease in the left ventricular ejection time, the mean rate of internal dimension shortening was significantly increased after both isosorbide dinitrate (from 1.07 ± 0.10 to 1.23 ± 0.11 sec^{-1} at 30 minutes [P <0.01] and to 1.13 ± 0.10 at 3.5 hours [P <0.05]) and nitroglycerin ointment (from 1.04 ± 0.09 to 1.15 ± 0.10 sec^{-1} at 30 minutes [P <0.05] and to 1.09 ± 0.09 at 4 hours [P <0.05]).

Each nitrate produced a large decrease in estimated left ventricular wall stress that was highly significant for 4 hours (Table II, Fig. 5). The maximal decrease was found at 2 hours after administration of isosorbide dinitrate (143.6 to 104.2 g/cm^2) (P <0.01) and at 1.5 hours

TABLE II

Echocardiographic Findings

Echocardiographic Variables	no.	Drug	Control	Hours 0.5	1.5	2	2.5	3.5	4	MAD mm	MAD %
EDD	11	I	52.4 ± 2.7	50.2 ± 2.7*	49.3 ± 2.9*	49.2 ± 2.9*	50.6 ± 2.8*	51.1 ± 2.8*	52.4 ± 3.0		
(mm)	10	N	52.6 ± 2.3	50.2 ± 2.5*	50.3 ± 2.3*	50.5 ± 2.4*	51.1 ± 2.4*	51.0 ± 2.4*	51.0 ± 2.6*		
	7	P	53.8 ± 3.2	54.1 ± 3.5	53.8 ± 3.4	53.5 ± 3.4	54.0 ± 3.5	54.0 ± 3.3	...	0.6	1.1
ESD	11	I	35.5 ± 3.2	32.7 ± 3.1*	32.9 ± 3.3*	32.7 ± 3.3*	33.1 ± 3.2*	33.7 ± 3.2*	35.5 ± 3.3		
(mm)	10	N	35.8 ± 3.2	32.8 ± 3.3*	32.8 ± 3.1*	33.1 ± 3.0*	33.4 ± 3.1*	34.3 ± 3.2*	34.3 ± 3.1*		
	7	P	36.3 ± 5.0	36.4 ± 4.9	36.5 ± 4.9	36.2 ± 5.1	36.2 ± 4.9	36.2 ± 4.8	...	0.5	1.5
PPD	11	I	48.4 ± 3.0	46.0 ± 3.0	45.8 ± 3.3*	45.4 ± 3.3*	47.3 ± 3.1*	46.9 ± 3.2*	48.5 ± 3.5		
(mm)	10	N	49.3 ± 2.7	46.7 ± 2.7*	46.4 ± 2.8*	46.2 ± 2.9*	47.1 ± 2.8*	47.6 ± 2.9*	47.5 ± 2.9*		
	7	P	50.7 ± 3.7	50.9 ± 4.0	50.5 ± 3.8	50.2 ± 3.8	50.7 ± 4.0	50.8 ± 3.8	...	0.9	1.8
Septum											
EDT	11	I	9.0 ± 0.5	9.6 ± 0.6†	9.8 ± 0.6*	10.0 ± 0.7*	9.7 ± 0.7*	9.5 ± 0.6*	9.5 ± 0.6*		
(mm)	10	N	8.3 ± 0.6	9.2 ± 0.6*	9.2 ± 0.6*	9.3 ± 0.5*	9.4 ± 0.6*	9.0 ± 0.5*	9.2 ± 0.6*		
	7	P	9.1 ± 0.5	8.9 ± 0.6	8.7 ± 0.5	8.9 ± 0.5	9.1 ± 0.4	9.1 ± 0.6	...	0.4	4.3
EST	11	I	11.9 ± 0.7	13.0 ± 1.0†	12.9 ± 0.9*	13.0 ± 0.9*	12.6 ± 0.8†	12.5 ± 0.9	12.6 ± 0.9		
(mm)	10	N	11.8 ± 0.7	12.2 ± 0.8	12.5 ± 0.8†	12.8 ± 0.8†	12.4 ± 0.8	12.4 ± 0.9	12.0 ± 0.8		
	7	P	12.3 ± 0.7	12.1 ± 0.7	12.2 ± 0.7	12.0 ± 0.7	12.3 ± 0.6	12.3 ± 0.7	...	0.5	3.7
PPT	11	I	9.9 ± 0.7	10.4 ± 0.7	10.5 ± 0.7	10.6 ± 0.7*	10.8 ± 0.8*	10.2 ± 0.7	10.3 ± 0.8		
(mm)	10	N	8.9 ± 0.5	9.8 ± 0.5*	10.0 ± 0.6*	10.2 ± 0.6*	10.0 ± 0.6*	10.2 ± 0.6*	10.2 ± 0.6†		
	7	P	9.4 ± 0.5	9.2 ± 0.6	9.1 ± 0.6	9.1 ± 0.6	9.4 ± 0.5	9.5 ± 0.6	...	0.4	2.8
Posterior wall											
EDT	11	I	8.2 ± 0.3	9.0 ± 0.4	8.9 ± 0.4	8.9 ± 0.3†	9.0 ± 0.4†	8.7 ± 0.4	8.6 ± 0.3		
(mm)	10	N	7.8 ± 0.4	8.8 ± 0.3*	9.0 ± 0.4*	8.7 ± 0.3†	8.4 ± 0.3†	8.6 ± 0.3*	8.7 ± 0.3*		
	7	P	8.6 ± 0.5	8.6 ± 0.4	8.5 ± 0.4	8.4 ± 0.4	8.7 ± 0.5	8.5 ± 0.4	...	0.4	4.8
EST	11	I	14.0 ± 0.6	15.0 ± 0.4*	15.3 ± 0.6*	15.2 ± 0.6*	15.5 ± 0.6*	15.4 ± 0.7*	14.6 ± 0.7		
(mm)	10	N	14.2 ± 0.5	15.3 ± 0.4*	15.5 ± 0.5*	15.1 ± 0.5*	14.9 ± 0.5*	15.1 ± 0.4*	14.7 ± 0.5		
	7	P	14.8 ± 0.5	14.8 ± 0.6	14.8 ± 0.5	14.6 ± 0.6	15.0 ± 0.6	14.8 ± 0.6	...	0.4	2.4
PPT	11	I	9.1 ± 0.2	9.9 ± 0.4	10.0 ± 0.5	10.0 ± 0.4†	10.2 ± 0.4†	9.9 ± 0.5	9.7 ± 0.4		
(mm)	10	N	8.8 ± 0.4	9.7 ± 0.3*	9.7 ± 0.3*	9.8 ± 0.2†	9.5 ± 0.3†	9.6 ± 0.2†	9.5 ± 0.2		
	7	P	9.4 ± 0.4	9.4 ± 0.4	9.4 ± 0.4	9.4 ± 0.5	9.4 ± 0.4	9.4 ± 0.3	...	0.4	4.7
% D	11	I	33.0 ± 2.9	36.1 ± 2.9*	34.8 ± 3.0*	34.7 ± 3.0*	35.7 ± 2.8	35.3 ± 3.0	33.3 ± 3.0		
	10	N	32.8 ± 3.1	34.5 ± 3.1	35.8 ± 3.0*	35.4 ± 3.1*	35.8 ± 3.2*	33.6 ± 3.3	33.7 ± 3.0		
	7	P	32.1 ± 4.9	33.0 ± 4.2	33.0 ± 4.2	32.1 ± 4.8	32.8 ± 4.3	32.8 ± 4.3	...	1.0	3.0
Vcf	10‡	I	1.07 ± 0.10	1.24 ± 0.11*	1.18 ± 0.11*	1.17 ± 0.11*	1.16 ± 0.10*	1.13 ± 0.10*	1.09 ± 0.09		
	10	N	1.04 ± 0.09	1.15 ± 0.10*	1.19 ± 0.10*	1.17 ± 0.10*	1.17 ± 0.10*	1.09 ± 0.10†	1.09 ± 0.09		
	7	P	1.06 ± 0.16	1.05 ± 0.12	1.05 ± 0.12	1.05 ± 0.13	1.07 ± 0.13	1.05 ± 0.14	...	0.04	3.8
Wall stress (g/cm^2)	11	I	143.6 ± 13.7	109.3 ± 10.9*	105.1 ± 10.9*	104.2 ± 12.2*	108.8 ± 12.7*	117.8 ± 13.6*	124.7 ± 15.1*		
	10	N	134.9 ± 12.6	104.0 ± 11.2*	98.7 ± 10.3*	100.2 ± 9.4*	104.2 ± 9.5*	105.7 ± 8.3*	111.2 ± 0.7*		
	7	P	118.1 ± 8.7	123.5 ± 9.0	121.6 ± 8.2	122.8 ± 9.8	122.0 ± 9.8	124.0 ± 8.7	...		

*$P < 0.01$.
†$P < 0.05$.
EDD = end-diastolic dimension; EDT = end-diastolic thickness; ESD = end-systolic dimension; EST = end-systolic thickness; I = isosorbide dinitrate; MAD = mean absolute difference between serial measurements after placebo; N = nitroglycerin ointment; no. = number of patients; P = placebo ointment; %D = percent internal dimension shortening; PPD = left ventricular dimension before the P wave of the echocardiogram; PPT = septal or posterior wall thickness before the P wave of the electrocardiogram; Vcf = mean rate of internal dimension shortening (circumferences/sec).
‡ In one patient after administration of isosorbide dinitrate a satisfactory carotid pulse tracing was not obtained for the calculation of Vcf.

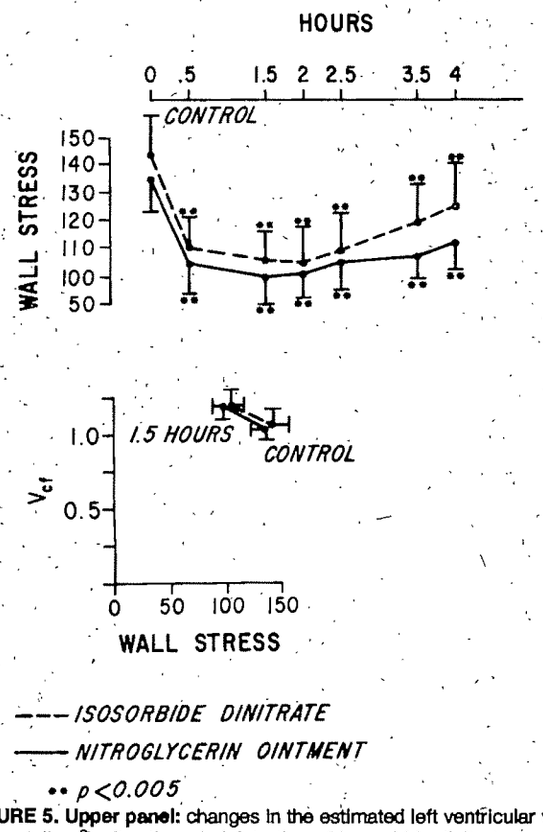


FIGURE 5. Upper panel: changes in the estimated left ventricular wall stress (g/cm^2) after the administration of isosorbide dinitrate and nitroglycerin ointment. **Lower left,** the decrease in wall stress was accompanied by an increase in the mean rate of internal dimension shortening (V_{cf}) expressed in circumferences per second. The control values and values at 1.5 hours after drug administration are shown. The sobars represent 1 standard error of the mean. p = probability.

after nitroglycerin ointment (134.9 to 98.7 g/cm^2) (P <0.01). No significant change in estimated wall stress, percent internal dimension shortening or mean rate of internal dimension shortening was observed after the application of placebo ointment.

Discussion

Improved left ventricular wall motion during nitrate therapy: Recent work from this institution and elsewhere suggests that sublingually administered nitroglycerin improves left ventricular segmental wall motion in man[5,7–13] and in the experimental animal.[4,6] However, there are no previous data indicating whether this improvement can be produced by the administration of long-acting nitrates and, if so, the duration of such a beneficial effect in man. The demonstration of improved left ventricular wall motion during nitrate therapy has stimulated clinical interest for several reasons. Helfant et al.[10] showed a good correlation between the ability of nitroglycerin to unmask reversible asynergy and the improvement in contractile function of the same sites after coronary bypass surgery. Apart from the potential value of this finding in predicting functional response to surgical revascularization, this finding suggests that the balance between myocardial oxygen supply and demand may be favorably altered in marginally ischemic zones of the left ventricle after nitroglycerin with improvement or restoration of systolic contraction, both as a result of improved blood supply to an area with abnormal wall motion and general unloading of the ventricle. This possibility has obvious therapeutic implications in the vasodilator treatment of angina pectoris and congestive heart failure associated with localized wall motion abnormalities.[20,21]

The results of our present study indicate that both isosorbide dinitrate and nitroglycerin ointment produce improvement in the velocity and extent of contraction of certain areas of the left ventricular wall, particularly segments with moderate impairment of function such as hypokinesia and asynchrony. The finding of a lesser effect on both normal sites and sites showing dyskinesia is in good agreement with results of previous studies using sublingually administered nitroglycerin.[4,7,10] All our patients had normal or near normal contraction of the high left ventricular sites (sites 1 and 2), but had various degrees of wall motion abnormalities involving one or both of the two lower sites (3 and 4). Not unexpectedly, therefore, function was enhanced to a greater extent in the lower than in the higher sites.

Mechanism of improved ventricular performance: The improvement in segmental wall motion could have been due to augmented global or regional contractility or to a decreased left ventricular afterload. The echocardiographic technique allowed assessment of the function of a left ventricular chordal dimension that was selected in identical fashion in all patients and reproduced as accurately as possible in the serial studies in each patient. We recognize the limitations of M mode echocardiography for measuring left ventricular dimensions (particularly at end-systole) and ventricular performance in patients with segmental left ventricular disease. Nevertheless, all of our patients had normal septal and posterior wall motion in the chord measured, all had a persistent reduction in ventricular dimensions, regardless of the location of previous infarction and all had improved amplitude and velocity of inward wall motion as demonstrated with wall motion videotracking. Furthermore, Abrams and Kochukashy[22] recently reported a similar reduction in left ventricular dimensions for at least 3 hours in normal subjects treated with nitroglycerin ointment. We therefore believe that *serial alterations* in left ventricular stress or afterload can be estimated from simultaneous measurements of arterial blood pressure and left ventricular echocardiographic dimensions and wall thickness in these patients.[23–25]

Quinones et al.[23] showed that echocardiography can be used to determine left ventricular stress-velocity relations in man and that normalized echocardiographic velocities correlated closely with cineangiographically measured velocities, even in the presence of localized asynergy.[26] We did not attempt to calculate the *peak* systolic wall stress in our study because the left ventricular pressure was unknown at that point, being intermediate between the arterial systolic and diastolic

pressure. However, we assumed that the peak arterial pressure was applicable during mid systole and we timed that point in the cardiac cycle as half the left ventricular ejection time. Other possibilities examined, such as estimating the wall stress in early systole, using the end-diastolic dimension and wall thickness and the diastolic blood pressure,[25] yielded drug-induced changes in afterload of a similar magnitude.

The persistent reduction in systolic blood pressure coupled with a decreased left ventricular dimension and increased wall thickness constitutes a marked decrease in afterload. Although our data do not exclude small changes in left ventricular contractility, isolated muscle studies by Zelis et al.[27] have failed to demonstate such a direct effect by nitroglycerin, and the absence of changes in heart rate indicates that indirect reflex enhancement of the inotropic state is unlikely. Thus, among the three main determinants of myocardial oxygen consumption, systolic wall tension was significantly decreased after the nitrates, whereas heart rate, and probably also contractility, was unchanged.[28] The hypothesis of a decrease in myocardial oxygen consumption is further supported by the significant decrease in the triple product after administration of each nitrate. The function of the individual segments of the left ventricular wall may have been enhanced by contracting against a smaller resistance and at a reduced metabolic cost rather than by increased regional perfusion although the latter mechanism cannot be excluded.

Cardiac output and stroke volume were not measured in our patients. However, significant changes of the latter are unlikely because the stroke excursion of the left ventricular dimension was unaltered by the three preparations.

Therapeutic implications: Uncertainty has existed regarding the efficacy and duration of action of long-acting nitrates. The work of Needleman et al.[29] in animals, supported by clinical studies[30] using oral isosorbide dinitrate in small doses (10 mg), suggested that oral administration of nitrates would result in their rapid degradation by hepatic enzymes with loss of vasodilator activity. However, our study confirms several recent reports[21,31–33] that isosorbide dinitrate given orally and sublingually[34,35] produces a beneficial hemodynamic effect that may last for several hours. Sustained symptomatic and hemodynamic benefits have also been reported to accrue from the application of nitroglycerin ointment in patients with angina pectoris[36–38] and congestive heart failure.[39] No significant discrepancies were found in our study between the modes of action of the two nitrates, and most of the affected variables remained significantly altered for 3 to 4 hours. Indeed, it is possible that with a longer study period an even more sustained duration of action could have been demonstrated.

Our study and previous work provide a firm basis for the clinical use of orally and topically administered nitrates in the treatment of selected patients with ischemic heart disease. Because their mechanism of action is similar, the choice between the preparations can be dictated by clinical convenience. Although orally administered isosorbide dinitrate is probably more convenient for outpatient use, the possibly longer duration of action of nitroglycerin ointment favors its use in hospitalized patients with angina pectoris at rest.

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Hemodynamic Effects of Intravenously Administered Quinidine On the Transplanted Human Heart

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The acute hemodynamic effects of intravenously administered quinidine were studied in five heart transplant recipients with an anatomically denervated heart. Quinidine, 10 mg/kg body weight, was infused over a 20 minute period, and mid wall left ventricular dynamics were measured with a new technique using metallic markers surgically implanted in the myocardial wall. Heart rate was maintained constant with atrial pacing, and aortic blood pressure was measured through an indwelling catheter. In each patient the hemodynamic responses to quinidine were similar. End-diastolic, end-systolic and stroke volumes decreased by an average of 19, 26 and 18 percent, respectively. Cardiac output decreased by a mean 0.92 liters/min (−18 percent), and the mean aortic blood pressure decreased by 10 mm Hg (−11 percent). All of these changes were statistically significant. Three indexes of the contractile state of the left ventricle—mean circumferential velocity, mean systolic diameter shortening and ejection fraction—were not significantly changed. We conclude that quinidine exerts no acute inotropic myocardial effects in the human transplanted heart and that, when given intravenously, its hemodynamic action is most consistent with venodilatation.

Reports of depressant hemodynamic effects have discouraged clinical use of quinidine by the intravenous route. However, quinidine's effects upon myocardial contractility in man have not been well defined. In isolated heart experiments and intact animal studies, some workers[1–4] have found a reduction in the force of myocardial contraction under the influence of quinidine. Others[5–7] have found either no change or an increase in contractile force due to quinidine, and still others[8–10] have described both negative and positive myocardial inotropic actions. Thus, the effects of quinidine on intrinsic myocardial performance remain controversial.

Most of the studies just cited have been limited by inadequate control of the effects of quinidine on autonomic nervous system activity (both cardiac and peripheral) as well as by use of drug doses that do not justify extrapolation to the clinical setting. Furthermore, examination of the action of quinidine in man has not included determinations of ventricular volumes and indexes of contractile state. We therefore evaluated the effects of intravenously administered quinidine on hemodynamic and left ventricular mechanical performance in recipients of human heart transplants with use of a new technique for measuring mid wall left ventricular dynamics. Heart transplant recipients provide a unique opportunity for studying the action of quinidine because of persistence of cardiac denervation after transplantation.[11,12]

Patients and Methods

Patients: Five heart transplant recipients were studied 8 to 20 months after transplantation at Stanford University Medical Center. Each patient gave signed written informed consent and the protocol was approved by the Stanford Human Subjects Committee. At the time of study, all patients had New York Heart

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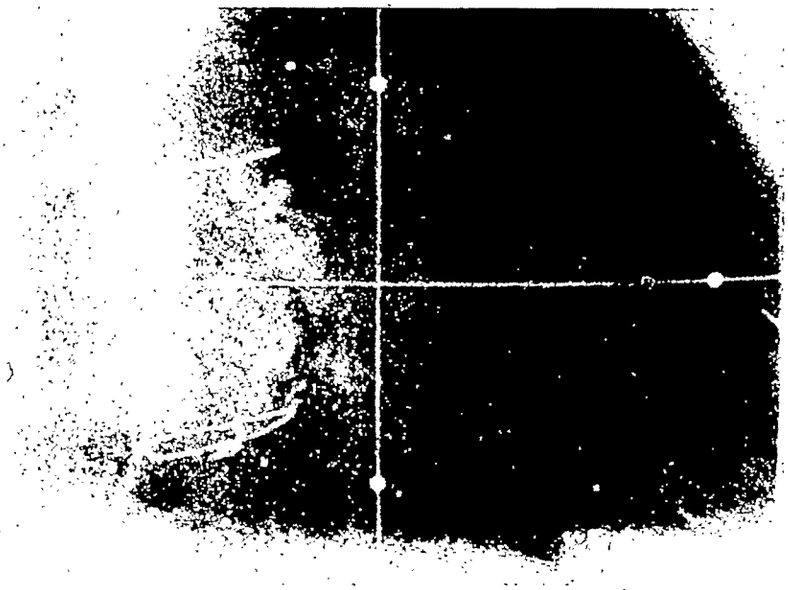


FIGURE 1. Cineradiographic frame showing seven left ventricular myocardial markers in a patient positioned in a 30° right anterior oblique projection for left ventriculography.

Association[13] class I functional status, and none was taking digoxin or antiarrhythmic agents.

At transplantation, seven miniature tantalum coils had been placed in the donor left ventricular mid wall in such a fashion as to outline the left ventricle as visualized in a 30° right anterior oblique projection.[14,15] The region of the aortic valve was marked with two adventitial silver clips placed in the same plane. Subsequent cineradiographic visualization of these markers (Fig. 1) allows quantitative determination of left ventricular segmental lengths, rate of change of length and volumes. Patients were studied with cardiac fluoroscopy, and the motion of the markers was recorded on an Ampex DR10A video disc at 30 frames/sec. The X-Y coordinates of the markers throughout three cardiac cycles were located on a frame by frame basis with a Tektronix light-pen system and converted to digital form. The digitized data were then transmitted to a CDC-6700 digital computer with stored programs for subsequent analysis of mid wall dynamics. Mid wall placement of the tantalum coils, achieved by using an inserter tool that allows the surgeon to determine accurately the depth of insertion,[15] results in entrapment of a volume of muscle of approximately 30 ml between the shell delineated by the markers and the endocardium. This volume remains constant during the cardiac cycle and does not interfere with the accuracy of volume determination.[16] Accuracy of these methods has previously been validated with demonstration of the system's ability to calculate known interpoint distances from a phantom placed in the radiographic system.[15] In addition, volumetric data determined with marker analysis correlated closely with data obtained with contrast ventriculography in six patients.[16] The average errors due to single plane approximation of three dimensional motions are small: 1.2 percent for mean systolic shortening and 0.05 circumferences/sec for velocity of contraction.[15] Accurate day to day reproducibility of data with this system has also been demonstrated.[15]

TABLE I

Hemodynamic Effects of Quinidine (group means ± standard errors of the means)

	Control	Quinidine	Percent Change	*P* Value*
Ventricular EDV (ml)	91.6 ± 14.8	73.2 ± 10.5	−19	<0.025
Ventricular ESV (ml)	39.4 ± 6.5	29.0 ± 4.8	−26	<0.02
Ventricular SV (ml)	52.6 ± 8.5	42.8 ± 6.3	−18	<0.05
Circumferential velocity (circumferences/sec)	0.98 ± 0.05	1.05 ± 0.04	+ 7	NS
Systolic diameter shortening (%)	22.7 ± 1.1	22.4 ± 1.3	− 2	NS
Ejection fraction (%)	57.6 ± 1.9	59.2 ± 3.2	+ 3	NS
Asynergy (%)	17.1 ± 1.8	21.5 ± 4.6	+23	NS
Cardiac output (liters/min)	4.96 ± 0.63	4.04 ± 0.50	−18	<0.025
Blood pressure (mm Hg)	91.4 ± 7.6	81.0 ± 6.5	−11	<0.005
SVR (units)	19.3 ± 3.8	19.7 ± 4.5	+12	NS
Heart rate (beats/min)	98.6 ± 5.6	95.2 ± 5.4	− 3	NS

*Student's paired *t* test (two-tailed).

EDV = end-diastolic volume; ESV = end-systolic volume; NS = not significant; *P* = probability; SV = stroke volume; SVR = systemic vascular resistance.

Hemodynamic measurements: The current studies were performed simultaneously with electrophysiologic investigations[17] during which intracardiac catheter electrodes were placed transvenously for control of the donor heart rate. The patients were studied in the postabsorptive state without sedation or under light sedation with diazepam. In addition to the electrode catheters, a PE no. 160 catheter was positioned in the central aorta by percutaneous insertion through the femoral artery; arterial blood pressure was measured with a Statham P23Db transducer connected to a Hewlett-Packard 88-11A signal conditioner and recorded photographically with a Hewlett-Packard physiologic recorder. A constant donor heart rate throughout the study was achieved by pacing at a cycle length 50 to 100 msec shorter than the original spontaneous cycle length. Control measurements consisted of systolic, diastolic and mean central aortic blood pressure (mm Hg), left ventricular end-diastolic, end-systolic and stroke volumes (ml), mean systolic circumferential velocity (circumferences/sec), mean systolic shortening (percent of mean end-diastolic diameter), ejection fraction (percent of end-diastolic volume), asynergy of contraction (percent)[18] and cardiac output (liters/min). Systemic vascular resistance was calculated as the ratio of mean aortic blood pressure to cardiac output, assuming a mean right atrial pressure of 5 mm Hg in all patients.

A freshly prepared quinidine gluconate salt solution of 5 percent dextrose and water (pH 6.17 at 22° C) was then administered through a peripheral vein by constant infusion over 20 minutes to a total dose of 10 mg/kg. Measurements of blood pressure and left ventricular dynamics were then repeated 5, 15 and 25 minutes after initiation of the quinidine infusion. Concentrations of plasma quinidine were assayed with the double extraction technique[19] 5, 15, 25, 30 and 40 minutes after the start of drug administration.

Results

Table I summarizes the group mean values during the control period and during administration of quinidine for mean arterial blood pressure, calculated total systemic vascular resistance, left ventricular volumes and ventricular function indexes. The values recorded as representative of drug response were the data points obtained at 25 minutes, a time when the mean plasma quinidine concentration had reached a plateau and was 4.37 ± 0.449 standard error of the mean μg/ml (range 3.07 to 5.14) (Fig. 2). At this time the QRS duration was not significantly altered; the mean Q-T interval for the group had increased from 318 ± 9 to 414 ± 19 msec. The hemodynamic variables measured showed a continued change from control levels between 5 and 15 minutes, but there was little change between 15 and 25 minutes, and the 25 minute values generally represented the maximal changes from the control level. During quinidine infusion, one patient reported a sensation of nausea of brief duration, but no other subjective or objective drug side effects occurred during or after the infusion.

Ventricular volumes (Fig. 3): Both end-diastolic and end-systolic volumes decreased significantly in all

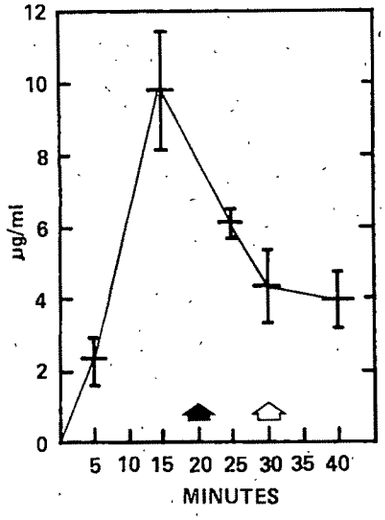


FIGURE 2. Mean plasma quinidine concentrations 5, 15, 25, 30 and 40 minutes after the beginning of quinidine infusion. The **closed arrow** indicates the termination of infusion and the **open arrow** the time at which repeat hemodynamic measurements were performed.

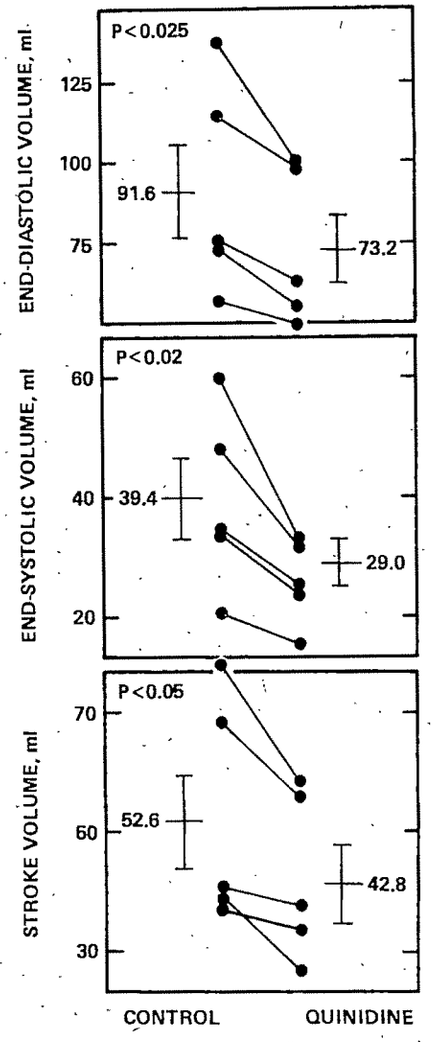


FIGURE 3. Effect of quinidine on end-diastolic, end-systolic and stroke volumes. A decrease occurred in all three measurements. Means, standard errors of the means and probability (P) values are indicated here and in subsequent figures.

five patients after quinidine. The mean decrease in left ventricular end-diastolic volume was 18.4 ml (−19 percent, $P < 0.02$). Because the mean decrease in end-systolic volume, although significant ($P < 0.02$), was smaller (−10.4 ml, −26 percent), mean stroke volume also decreased after quinidine (−9.8 ml, 18 percent, $P < 0.05$).

Ventricular function indexes (Fig. 4): Mean circumferential fiber shortening rate at the left ventricular mid wall was not significantly altered by quinidine; no large changes in this index occurred in any patient. Mean percent diameter shortening during systole and the ejection fraction were also unaffected. Asynergy of ventricular contraction (not shown in the figure) was increased, but the change was not statistically significant.

Cardiac output (Fig. 5): All five patients exhibited a reduction in cardiac output after administration of quinidine. The average decrease of 0.92 liters/min (−18 percent) was significant ($P < 0.025$).

Blood pressure (Fig. 5): Mean aortic pressure decreased after quinidine in all five patients; the average reduction was 10.4 mm Hg (−11 percent, $P < 0.005$).

Calculated total systemic vascular resistance (Fig. 5) was not significantly altered because decreases in mean arterial pressure were accompanied by proportionate reductions in cardiac output. However, the calculated change in systemic vascular resistance may be slightly in error because of the assumption of a constant right atrial pressure.

Heart rate was slightly but insignificantly decreased by quinidine (Table I).

Discussion

Quinidine and the contractile state of the heart: Human heart transplant recipients were used as subjects in this study of the hemodynamic effects of quinidine in order to eliminate the variable of neurally mediated reflex effects of quinidine on myocardial performance. Heart rate was also maintained constant, and the selected drug dose resulted in plasma quinidine concentrations in the range considered therapeutic for long-term oral administration.[19] Consistent effects were observed in all five patients: Left ventricular diastolic

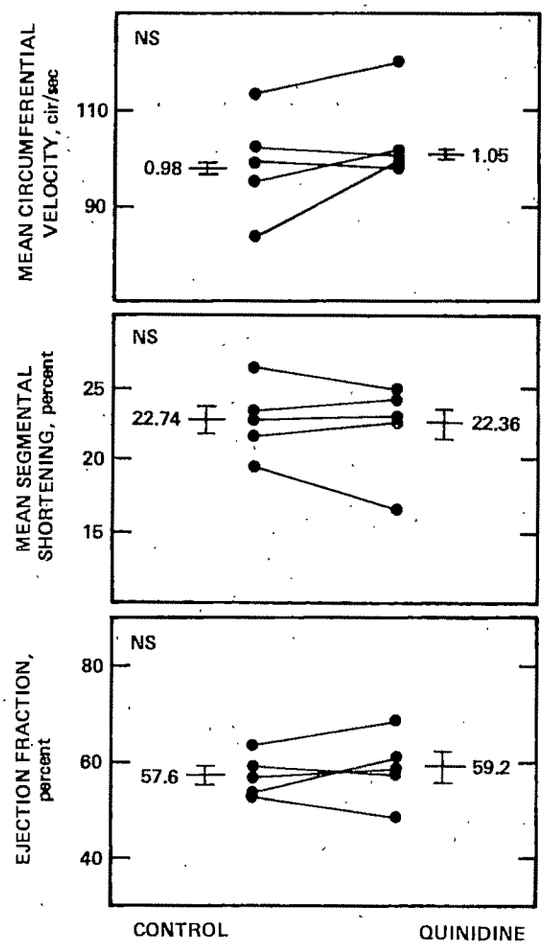


FIGURE 4. Effect of quinidine upon three indexes of ventricular contractility. No significant change (NS) was observed. cir = circumference.

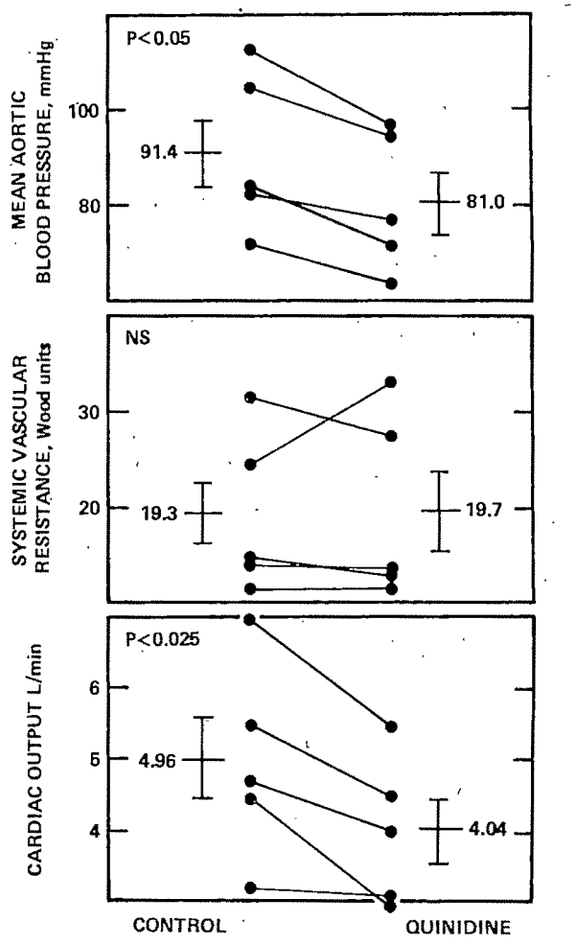


FIGURE 5. Effect of quinidine on mean aortic blood pressure (**upper panel**) and cardiac output (**lower panel**) and calculated systemic vascular resistance (**center panel**). The latter was unchanged, but the former two variables decreased significantly. L = liter; NS = not significant.

and systolic volumes, as well as stroke volume and cardiac output, decreased; mean arterial blood pressure was mildly reduced and systemic vascular resistance was unaffected. No significant effects upon left ventricular contractile state, as indicated by velocity, synchrony and extent of left ventricular contraction, were observed.

The reduction in preload (decreased end-diastolic volume) consequent to quinidine administration, in the absence of any other drug effect, would have produced a decrease in the extent and velocity of contratction. On the other hand, the mild decrease observed in left ventricular afterload (diminished systolic pressure and chamber size) after quinidine should have produced an apparently positive inotropic effect. The extent to which these opposing effects canceled one another in our experiment cannot be determined; however, the recorded changes in ventricular volumes and blood pressure, although statistically significant, were relatively small. In addition, offsetting effects of circulating catecholamines upon myocardial contractility were not excluded in our investigation; however, it is unlikely that such a response occurred over the short duration of the study, and the absence of a significant change in heart rate supports this contention. Thus, we infer that intravenously administered quinidine exerts no important acute inotropic effects on the denervated transplanted human heart. Furthermore, even if there were a significant interaction of myocardial contractility with preload, afterload or humoral influences, the lack of a *net* myocardial depressant effect is the *clinically* important finding.

Previous in vitro and in vivo studies of the effect of therapeutic levels of quinidine upon the contractile state of the myocardium have produced conflicting results. For example, Kruta et al.[9] concluded that negative inotropic effects of quinidine on guinea pig and rat atria in vitro resulted from the drug's negative chronotropic action since positive inotropy occurred with pacing. Kennedy and West[10] also found a cycle length dependency for quinidine's inotropic effects, but in the reverse of those observed by Kruta et al.; they furthermore described positive inotropic effects with quinidine concentrations in vitro as high as 50 μg/ml, but consistently negative effects at higher concentrations. However, in all of their experiments, the quinidine concentrations were in excess of those considered to be within a clinically therapeutic range. On the other hand, Tomoda et al.,[2] using isolated muscle preparations, found negative inotropic effects in the presence of "therapeutic" concentrations of quinidine. Stern[4] also found consistent negative effects of quinidine upon contractile state, with the use of a "therapeutic" quinidine dose of 3.5 mg/kg given intravenously to open chest dogs. In another preparation used in short-term animal studies, Pruett and Woods[8] reported a positive inotropic action of quinidine at a relatively high infusion rate of 1 mg/kg per min, but negative effects at higher rates. Angelakos and Hastings[1] also detected a negative inotropic action, but only if the quinidine infusion rate exceeded 0.4 mg/kg per min or if the total dose exceeded 15 mg/kg at rapid infusion rates or 28 mg/kg at slower rates. In a study in man, Ferrer et al.[5] concluded that therapeutic plasma levels of quinidine exerted no negative effects upon myocardial contractile state and that the hypotensive action of the drug was due solely to peripheral vascular effects.

Autonomic nervous system influences and cardiac effects of quinidine: Darby et al.[6] raised the question of autonomic nervous system influences upon the overall cardiac effects of quinidine. They reported that positive myocardial inotropic effects were abolished in both anesthetized and conscious dogs when sympathetic blockade was induced; they concluded that reflex sympathetic responses to systemic hypotension accounted for positive inotropic effects under the influence of quinidine. There is additional evidence that quinidine produces not only reflex sympathetic responses,[20] but also direct beta adrenergic blocking actions[21] and vagolytic effects.[22–25]

Confusion as to the true direct effects of quinidine upon myocardial contractility is due in part to interstudy variability in dose of quinidine used, the timing and nature of measurements of ventricular contractility and variations in degree of control over both autonomic nervous system activity and direct peripheral vascular changes caused by quinidine. A recent study from our laboratory[7] has helped to clarify some of these issues. The myocardial inotropic effects of quinidine given in therapeutic doses were studied in 18 dogs under chloralose anesthesia after pharmacologic sympathetic blockade and surgical section of the vagi. Left ventricular preload, arterial pressure and heart rate were maintained constant. In this setting, quinidine exerted no direct effects on myocardial contractility.

Peripheral vascular effects of quinidine: Our findings in this study of human heart transplant recipients are in agreement with our observations in the canine model. However, despite absence of any measurable effects of quinidine on left ventricular contractile performance, significant hemodynamic and mechanical changes did occur. Arterial blood pressure, left ventricular volumes and cardiac output all decreased. These alterations are consistent with a predominant peripheral vascular effect of quinidine.

The peripheral vascular action of quinidine has been widely studied. The drug appears to possess both direct vasodilator and alpha adrenergic blocking properties.[26] The adrenergic blocking action of quinidine has been documented to occur both in the arterial and in the venous systems.[27] Thus, within the context of these known peripheral effects of quinidine, the decreases in left ventricular volume and cardiac output in our patients can best be explained by an increase in venous capacitance resulting in diminished venous return.

Clinical implications: Although quinidine does not appear to produce myocardial depression directly, it may exert complex effects upon both the cardiac and the peripheral autonomic nervous systems and may produce direct peripheral vasomotor changes. Thus, adverse hemodynamic effects may result, as evidenced by the significant decreases in cardiac output in our subjects. Patients with congestive heart failure may be

especially susceptible to such unfavorable hemodynamic effects of quinidine, inasmuch as previously documented blunted autonomic responsiveness in such patients[28–30] removes their ability to adjust cardiac function reflexly and renders them physiologically similar to our patients with an anatomically denervated heart. Although our heart transplant recipients did not experience serious hemodynamic deterioration after quinidine, the condition of critically ill patients might be significantly compromised by quinidine's peripheral vascular effects.

We conclude from this study of the effects of quinidine on the denervated transplanted human heart that in therapeutic intravenous doses the drug produces no direct positive or negative inotropic effects. However, it does cause a measurable reduction in cardiac output, an action best explained by peripheral venodilatation.

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Blood Pressure, Renin Activity and Heart Rate Changes During Propranolol Therapy of Hypertension

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To investigate the importance of plasma renin activity in determining the antihypertensive action of propranolol and of heart rate in guiding propranolol therapy, the effect of a graded oral dose of propranolol on blood pressure, plasma renin and heart rate was studied in 24 men with essential hypertension and differing initial levels of renin activity. Although plasma renin decreased substantially in patients with normal and high renin levels taking a small dose of propranolol (40 mg/day), blood pressure was unchanged in the normal renin group, and a small decrease in systolic pressure alone was noted in those with high plasma levels of renin. Patients with low renin levels had no reduction in blood pressure with small doses of propranolol, but as a group they responded well to a dose of 320 mg/day. Standing heart rate decreased maximally at plasma propranolol concentrations greater than 25 ng/ml, and did not exceed 72 beats/min with plasma concentrations above that level. Overall, the observed responses for plasma renin and heart rate were more pronounced at lower plasma propranolol concentrations than those for blood pressure.

The beta adrenergic receptor blocking agent propranolol is an effective antihypertensive agent.[1] The mechanism of this action has been vigorously pursued, with the major sites of interest being the heart,[2] the brain[3] and the kidney. The latter has received considerable attention, primarily because of the work of Bühler, Laragh and associates.[4] Building on the fact that renin release is inhibited by propranolol[5] and the assumption that angiotensin II is a major factor in determining peripheral resistance in patients with hypertension, these investigators have postulated that propranolol reduces blood pressure because it decreases renin activity. They suggest, as a corollary, that the level of renin activity in a given hypertensive patient is an important predictor of responsiveness to propranolol.[4] However, Hansson and Zweifler[6] observed that although plasma renin activity decreased substantially in a group of patients treated with propranolol, 320 mg/day, blood pressure reduction was not invariable. Other studies have also raised serious doubts that propranolol[7] and other beta adrenergic blocking drugs[8,9] are antihypertensive because of their effect on plasma renin activity. The present study was designed to compare changes in plasma renin, heart rate and blood pressure produced by small doses of propranolol as well as a dose of 320 mg/day in a group of hypertensive patients with differing initial levels of renin activity.

Material and Methods

Study population: Twenty-four patients with essential hypertension were recruited from the hypertension clinics of the University of Michigan Medical Center and the University of Michigan Health Service. All were men aged 20 to 60 years and had casual clinic-recorded blood pressures greater than 150 mm Hg systolic or 90 mm Hg diastolic, or both, after at least 2 weeks of no medication other than placebo. Patients with diastolic pressure greater than 125 mm Hg, grade III or IV retinopathy, or serum creatinine concentration greater than 2.0

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TABLE I

Blood Pressure, Renin Activity and Plasma Propranolol Concentration in Three Plasma Renin Categories Before and During Administration of Propranolol (mean values ± standard error of the mean)

PRA	Placebo			Propranolol, 40 mg/day				Propranolol, 80 mg/day				Propranolol, 320 mg/day			
	BP			BP				BP				BP			
	S	D	PRA	S	D	PRA	PPL	S	D	PRA	PPL	S	D	PRA	PPL
Normal (no. = 11)	157.0 ± 3.7	101.9 ± 3.3	2.40 ± 0.19	152.8 ± 3.7	100.3 ± 3.0	1.45 ± 0.25	1.9 ± 1.1	146.5 ± 2.4	97.0 ± 2.1	1.07 ± 0.15	19.6 ± 11.0	132.8 ± 1.5	89.6 ± 1.9	0.86 ± 0.22	157.0 ± 36.9
Low (no. = 6)	173.3 ± 5.3	107.3 ± 4.7	0.96 ± 0.12	175.3 ± 8.4	107.0 ± 3.8	0.66 ± 0.24	1.0 ± 0.6	163.3 ± 9.3	99.0 ± 6.8	0.72 ± 0.17	20.4 ± 9.7	144.3 ± 10.2	90.0 ± 5.0	0.46 ± 0.11	94.2 ± 24.2
High (no. = 7)	161.3 ± 3.1	90.4 ± 2.4	4.32 ± 0.22	148.6 ± 2.9	85.6 ± 4.3	0.47 ± 0.18	6.9 ± 3.3	144.3 ± 2.6	83.4 ± 3.8	1.40 ± 0.22	16.5 ± 4.4	135.4 ± 1.8	80.0 ± 2.5	1.60 ± 0.27	120.0 ± 21.4

BP = blood pressure (mm Hg); D = diastolic; PPL = plasma propranolol (ng/ml); PRA = plasma renin activity (ng/ml per hour); S = systolic.

mg/100 ml were not considered for the study. Secondary causes of hypertension were excluded by thorough clinical examination and laboratory studies including rapid sequence intravenous urography and measurement of urinary aldosterone excretion.

All patients were told of the investigative nature of the study and read and signed a consent form outlining the details of the tests to be performed.

Renin categorization: A 24 hour urinary sample for determination of sodium was collected in a metabolic ward after the patient had been maintained on a 160 mEq sodium diet for at least 5 days. Blood for plasma renin estimation was drawn in the morning after 1 hour of standing. Plasma was separated in a refrigerated centrifuge, stored at −20° C, and plasma renin activity was estimated within 2 months by radioimmunoassay.[10] A nomogram relating plasma renin activity during standing to 24 hour urinary sodium excretion[11] was developed from measurements in 41 age-matched normal male volunteers. Patients were categorized into normal, high and low renin groups by referring their plasma renin values to the limits of normality defined by the nomogram. In patients with low plasma renin, renin activity subsequently remained suppressed after 6 days of sodium deprivation (10 mEq sodium daily). Plasma renin activity was elevated in 7 patients, normal in 11 and low in 6. This distribution was a consequence of selective recruitment for the study, based on previous plasma renin typing, in an effort to obtain an adequate number of patients in each renin subgroup.

Drug trial: Patients were given placebo for 2 weeks, then given propranolol in the following doses: 10 mg four times daily for 4 weeks, 20 mg four times daily for 4 weeks and 80 mg four times daily for 4 weeks. At the end of each treatment period patients returned in the morning, were examined and had blood drawn after 1 hour of standing for determination of plasma renin activity and plasma propranolol level (2 to 3 hours after the last dose of propranolol). Plasma propranolol concentration was measured fluorometrically.* [12] Blood pressure and pulse rate were determined on each visit by the same observer (M.E.) after 3 minutes of recumbency and 1 minute of standing.

Results

Blood pressure response and renin activity: During placebo therapy, patients with low plasma renin had a slightly higher mean blood pressure ($P < 0.05$; (analysis of variance [Sheffé method]) than those in the other two renin categories (Table I) and those in the high plasma renin group had lower mean and diastolic pressures ($P < 0.05$). Treatment with propranolol in a dose of 40 mg/day caused no significant reduction of blood pressure in patients with a normal or low renin level, but systolic blood pressure decreased ($P < 0.01$, paired t test) in the high renin group (Fig. 1). Propranolol in a dose of 80 mg/day produced a significant decrease in blood pressure in patients with normal renin and a further reduction in those with high plasma renin, but had no effect in the low renin group. A substantial reduction in blood pressure occurred in patients in all three renin categories during treatment with propranolol in a dose of 320 mg/day.

Plasma renin activity (Table I) decreased significantly ($P < 0.01$, paired t test) and substantially during administration of propranolol, 40 mg/day, in patients

* Courtesy of Ayerst Laboratories.

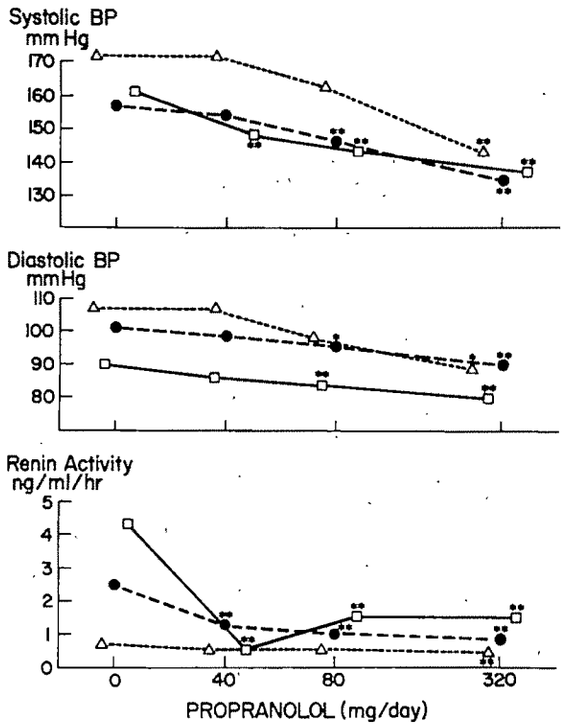


FIGURE 1. Changes in recumbent blood pressure (BP) and upright plasma renin activity during propranolol therapy in three renin categories: low renin **(triangles)** (no. = 6); normal renin **(closed circles)** (no. = 11); high renin **(squares)** (no. = 7). Significance of change from control value (paired *t* test): * = *P* (probability) <0.05; ** = *P* <0.01.

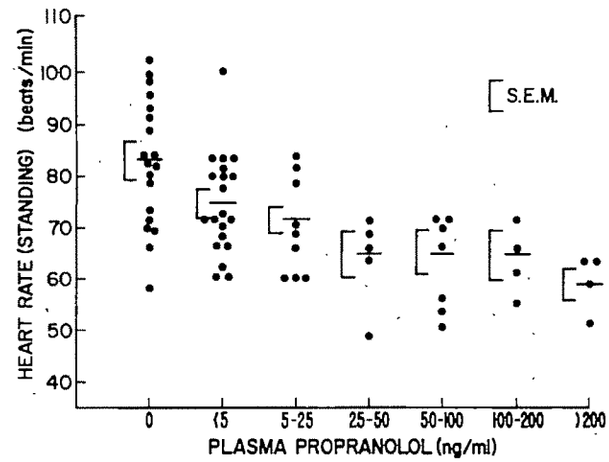


FIGURE 2. Standing heart rate before and during propranolol therapy related to plasma propranolol concentration. S.E.M. = standard error of the mean.

with a normal or high renin level. Larger doses of the drug were accompanied by a further decrease in renin activity in patients in the normal renin group, but an increase in renin levels in patients in the high renin group (Fig. 1). In the low renin group, renin activity decreased significantly only at the dose of 320 mg/day.

A positive correlation between change in blood pressure and change in plasma renin activity during treatment with propranolol in a dose of 40 mg/day was observed only in the high renin group, and in this group the linear correlation coefficient was only 0.34 ($P > 0.05$). A statistically significant correlation between reduction in blood pressure and decrease in renin activity also was not found in any of the patient groups during the 80 mg/day treatment period. At 320 mg/day the correlation coefficients were as follows: normal renin 0.41 ($P > 0.05$), low renin 0.34 ($P > 0.05$) and high renin 0.78 ($P < 0.05$). Plasma propranolol concentrations were similar in all three renin subsets at the various administered doses of the drug (Table I); although the concentrations ranged from 1 to 6.9 ng/ml during administration of propranolol (40 mg/day), the differences between groups were not statistically significant.

Heart rate response and renin activity: Heart rates in the normal and low renin groups were similar, and were slower than in patients with high renin activity (Table II), but this difference was statistically significant ($P < 0.05$) only for standing heart rate. Propranolol in a dose of 40 mg/day had no significant effect on heart rate in patients with low renin activity but had a dramatic effect on those with a high renin activity; the normal renin group demonstrated a moderate response. Further slowing of the heart was observed in the high and normal renin groups during treatment with 80 mg/day. In a dose of 320 mg/day propranolol produced cardiac slowing in all patients, and heart rates in all renin groups were similar at the end of this treatment period. Standing heart rate paralleled propranolol dose more closely than recumbent heart rate, particularly in the normal renin group. Definite cardiac slowing was

TABLE II

Supine and Standing Heart Rates in Three Plasma Renin Categories Before and During Administration of Propranolol (mean values ± standard error of the mean)

	Placebo		Propranolol, 40 mg/day		Propranolol, 80 mg/day		Propranolol, 320 mg/day	
PRA	Supine HR	Standing HR	Supine HR	Standing HR	Supine HR	Standing HR	Supine HR	Standing HR
Normal (no. = 11)	71.1 ± 3.9	82.9 ± 3.8	66.0* ± 3.0	74.9* ± 4.1	64.9* ± 2.8	70.8† ± 3.6	56.4† ± 2.2	59.9† ± 2.8
Low (no. = 6)	63.8 ± 4.7	79.8 ± 5.2	63.0 ± 3.9	72.0 ± 5.1	58.8 ± 3.7	69.9 ± 4.0	53.5† ± 2.4	57.3† ± 3.1
High (no. = 7)	79.1 ± 3.4	96.6 ± 4.0	63.4† ± 1.9	75.0† ± 2.1	59.4† ± 1.9	69.3† ± 2.9	56.7† ± 2.6	62.9† ± 1.8

*$P < 0.05$; †$P < 0.01$ (significant change from placebo value [paired *t* test]).
HR = heart rate; *P* = probability; PRA = plasma renin activity.

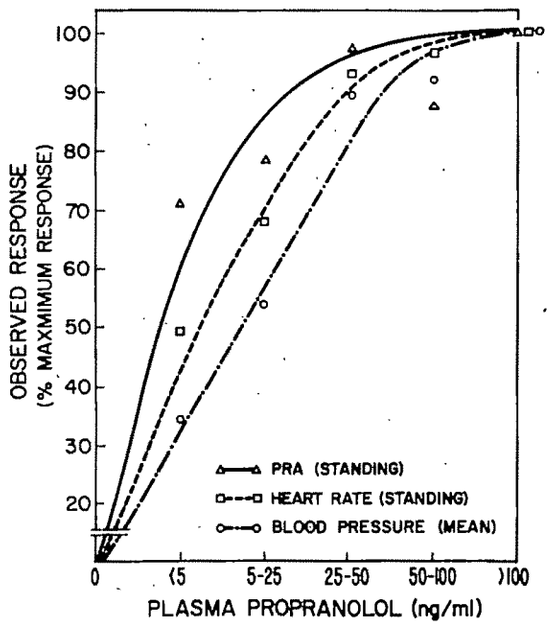


FIGURE 3. Percent of maximal observed response of blood pressure, plasma renin activity (PRA) and heart rate related to plasma propranolol concentration.

apparent at very low *plasma* propranolol levels and a maximal effect was achieved with concentrations of 25 to 50 ng/ml (Fig. 2). A standing heart rate greater than 72 beats/min was not observed with a plasma propranolol concentration greater than 25 ng/ml.

Correlation with propranolol plasma levels: When expressed as percent of maximal observed response, blood pressure achieved 37 percent of its total change during propranolol therapy at plasma propranolol levels of less than 5 ng/ml (Fig. 3). By contrast, the plasma renin response was 78 percent of maximum at a plasma propranolol level of less than 5 ng/ml and the heart rate response was 49 percent of maximum at the same plasma level. The dose-response curves for plasma renin and heart rate became almost flat with concentrations of 25 to 50 ng/ml, as did the blood pressure curve with concentrations of 50 to 100 ng/ml.

Discussion

Correlation of plasma renin levels and blood pressure response to propranolol: The results of this study reveal a dissociation between change in blood pressure and change in plasma renin activity during administration of small doses of propranolol to patients with essential hypertension. Renin activity did decrease substantially in patients with normal and high renin levels taking propranolol in a dose of 40 mg/day. However, blood pressure did not decrease in the normal renin group, and only a modest decrease in systolic pressure was observed in patients with a high plasma renin level; and within the latter group, the correlation between change in blood pressure and change in plasma renin activity was not statistically significant. These findings therefore tend to refute the hypothesis[4] that propranolol decreases blood pressure because it decreases renin activity and are consistent with earlier[5] and more recent[13] findings. The differing dose-response relations of blood pressure, plasma renin and heart rate to plasma propranolol concentration are additional evidence against the "renin hypothesis" and add weight to the similar finding of Leonetti et al.[14] Our data differ from those of Hollifield et al.,[15] who observed a decrease in blood pressure in normal renin hypertensive patients taking propranolol in a dose of 40 mg/day, with a significant correlation between change in pressure and change in renin activity at that dose. This discrepancy is unexplained, but perhaps is due to differences in case selection or renin categorization. Nevertheless, it is difficult to accept the interpretation of Hollifield et al. of their results during small dose propranolol therapy. The degree of correlation they observed was not high enough to establish a cause and effect relation between blood pressure reduction and decrease in plasma renin activity.

Our study lends some support to those who believe that renin activity may have some value in predicting the antihypertensive response to propranolol therapy,[4,14] but only at low dose levels. Blood pressure decreased modestly in patients with a high renin level taking propranolol in a dose of 40 mg/day and not at all in patients with a low or normal renin level given the same dose. This difference is probably related to the fact that our high renin group represents a special subset of patients with essential hypertension who have increased sympathetic nervous system activity.[16] Nevertheless, it is important to point out that blood pressure decreased substantially in all three groups of patients when taking 320 mg/day of propranolol. This latter observation is compatible with previous data[15,17] and consistent with the concept that propranolol is capable of decreasing blood pressure through some mechanism other than suppression of the renin-angiotensin system.

Correlation of plasma renin levels and heart rate response to propranolol: The data relating change in heart rate to dose of propranolol reveal that (1) substantial cardiac slowing occurs with a small dose of propranolol in patients with normal and high renin activity; (2) cardiac slowing in patients with normal and high renin activity is related to the dose of propranolol administered; and (3) patients with high renin activity are more sensitive and those with low renin activity less sensitive to the chronotropic effects of propranolol than those with normal renin activity. This finding may be related to diminished sympathetic nervous system activity in those with a low renin level[18] and to heightened activity in the high renin group.[16]

Plasma propranolol concentrations of more than 25 ng/ml were always accompanied by standing heart rates of less than 72 beats/min. Because the dose-response curve for change in heart rate in relation to plasma propranolol concentration is to the left of that seen with

change in blood pressure (that is, slowing of heart rate occurs at a lower plasma propranolol concentration than that causing a decrease in blood pressure), absence of a heart rate effect in patients with a suboptimal blood pressure response during propranolol therapy indicates inadequate plasma levels of propranolol. If blood pressure has not normalized during treatment with propranolol alone and the standing heart rate is greater than 72/min, the dose of propranolol should be increased.

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TQ-ST Segment Mapping: Critical Review and Analysis of Current Concepts

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Controversy and confusion surround many aspects of TQ-ST segment mapping today. Technical standards pertaining to the recording and measurement of the TQ-ST deflection have not been uniformly established nor has the correlative value of the deflection as an indicator of myocardial injury been clearly ascertained. The TQ-ST deflection is believed to originate primarily although not exclusively as a result of extracellular potassium accumulation in the ischemic region and subsequent establishment of a transmembrane potential gradient during diastole and systole at the ischemic boundary. Nonspatial factors (including electrolytes, antiarrhythmic agents, heart rate) influence the TQ-ST deflection by altering this gradient. Spatial factors (including ischemic area and shape, electrode location) alter the relative position of the ischemic boundary to the electrode site and as such can be analyzed with the solid angle theorem.

Further study of the complex behavior of the TQ-ST segment deflection, particularly in the presence of pharmacologic intervention, is necessary before mapping techniques can be used reliably in clinical studies designed to quantitate and modify ischemic damage.

> "We must determine more exactly what the different electrocardiographic patterns seen in infarction mean in terms of the size of the infarct, its location, and the character of the changes in the muscle involved."[1]

Techniques currently used to assess ischemic or infarcted myocardium in patients include hemodynamic monitoring, creatine kinase (CK) activity curve analysis, myocardial radionuclide imaging and precordial TQ-ST segment mapping. The latter has enjoyed considerable popularity recently primarily because of its low cost noninvasive approach and simply applied rules of interpretation. However, despite the large number of studies employing this technique, the complex relation between the TQ-ST segment deflection and the underlying ischemic region has not been clearly defined. Consequently, some disagreement over the specificity and quantitative value of this electrocardiographic indicator of myocardial injury has developed.[2–10] In this review we have critically examined the TQ-ST segment, its historical development, current methods for recording and measuring the deflection, the nomenclature used in its characterization, its theoretic basis and finally its modification by changes in ischemic geometry and pharmacologic intervention.

Historical Perspective

Some controversy has surrounded the TQ-ST segment deflection since its first description by Englemann[11] nearly 100 years ago. In 1889 Waller[12] regarded the deflection as a normal phenomenon, but Bayliss and Starling[13] showed that it was indicative of cardiac injury. After the discovery by Pardee[14] in 1920 of TQ-ST segment changes in patients after acute myocardial infarction, research in this area intensified. After Einthoven's establishment of the standard limb lead

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system,[15] it was soon recognized that electrode location as well as the area of injury was capable of influencing both the magnitude and polarity of the TQ-ST segment deflection.[16–20] For some time these experimental studies ran parallel to the theoretical formulations of Gauss,[21,22] Helmholtz,[23] Maxwell[24] and others,[25–30] which laid the groundwork for our present understanding of all electrical phenomena.

In 1933 Wilson et al.[31] recognized the applicability of these principles—particularly the solid angle theorem—to the solution of numerous problems of electrocardiographic interpretation. While dealing initially and primarily with the relation of the TQ-ST segment to cardiac injury, Wilson et al.,[1,31] Bayley[32] and others[33,34] soon broadened their approach, applying the same physical principles to the QRS complex and the T wave, and to their modifications by infarction, hypertrophy and conduction abnormalities.

Controversy concerning the TQ-ST segment deflection centered upon (1) whether the abnormal deflection reflected electrical changes occurring primarily during diastole or during systole in the ischemic tissue, and (2) the mechanism by which injury or ischemia brought about such changes. A survey of the most recent literature[6,35–37] reveals that these issues are still unresolved (see Addendum A). Although first thought by Lillie[30] in 1922 to be due to depolarization of the ischemic cell and therefore a diastolic event, Sugarman et al.[38] in 1940 proposed that "S-T segment elevation" was actually a combination or summation of T-Q segment depression and S-T segment elevation. The controversy was thoroughly reviewed and apparently resolved by Samson and Scher[39] in 1960 in a series of experiments in which direct current intracellular and extracellular electrograms were recorded simultaneously during acute coronary occlusion and "S-T segment elevation" was shown to have both diastolic and systolic components. The recent (1975) magnetocardiographic experiments of Cohen and Kaufman[35] challenge this view, again suggesting that the deflection is, at least early in ischemia, primarily a diastolic event.[40]

Although its use in studies dealing with ventricular activation[41] and recovery[42] has continued, interest in describing the TQ-ST segment deflection in terms of solid angle theory generally subsided after the deaths of Wilson (1952) and Bayley (1969). After the elucidation of the various determinants of myocardial oxygen consumption, Braunwald[43] pointed out that the use of agents in acute myocardial infarction that either increased coronary blood flow or decreased oxygen demands might be helpful in limiting eventual infarct size. Subsequent studies suggested that infarct size was an important determinant not only of ventricular pump failure[44–46] but also of arrhythmias.[47,48] Thus the need for methods to estimate ischemic damage and for agents capable of limiting that damage became apparent. In response, Maroko et al.[49–51] and others[52,53] soon introduced the techniques of epicardial and precordial TQ-ST segment mapping.

Technical Considerations

Mapping Techniques

Various epicardial and precordial techniques have been used in mapping studies. Epicardial electrodes can be classified as either traumatic or atraumatic. The traumatic electrodes, including hooks, wire sutures and needles inserted into the epicardium,[54] usually result in the immediate evolution of large TQ-ST segment deflections that gradually return to or near an isoelectric position in 30 to 60 minutes.

The atraumatic electrodes comprise two categories. The "free" electrodes consist of either a saline wick[50,55–57] or a bare wire[58] held manually by the investigator at a position on the epicardial surface bearing some relation to a specific anatomic landmark (for example, bifurcation of coronary arteries and veins). This method requires that mechanical stress exerted by the electrode on the epicardium be kept to a minimum to avoid the introduction of artifactual TQ-ST deflections. With such a method it is improbable that motion of the heart permits strict localization of the electrode to a single point on the epicardial surface during the course of the cardiac cycle. Hence the T-Q segment may be recorded during diastole from one position and the S-T segment during systole from another (an indeterminable distance away).

TABLE I

Measurement of TQ-ST Segment Deflections*

Investigator	Criteria		Amplifier (hertz)
	Diastole†	Systole	
Reid et al.[52]	T-P or P-Q segment	60 msec after nadir of S wave	...
Madias et al.[53]	T-P or P-Q segment	60 msec after nadir of S wave	...
Nielsen[2]	T-P	60 msec after nadir of S wave	...
Hornsten and Bruce‡[62]	P-Q	54 and 74 msec after nadir of S wave	0.06–100
Bruce et al.‡[63]	P-Q	40 and 60 msec after nadir of S wave	...
McHenry et al.‡[64]	P-Q	60 msec after peak R wave	...
Reid et al.[65]	T-P	120 msec after peak R wave	...
Redwood et al.[54]	...	100 msec after onset of QRS complex	...
Muller et al.[4]	T-P	20 msec after end of QRS complex	...
Goldberger[66]	T-P	40 msec after end of QRS complex	...
Grewin[67]	P-Q	50 msec after end of QRS complex	0.10–600
Akiyama et al.[68]	P-Q	20 and 60 msec after end of QRS complex	...
Holland and Brooks[69]	P-Q	Lowest point of S-T segment/inflection point	0.15–300
Parisi et al.[70]	T-P	Lowest point of S-T segment	...
Bruyneel[57]	T-Q	Mid point of S-T segment/parallel portion of S-T	DC to 1000
Becker et al.[58]	...	Mid point of S-T segment	...
Blomquist‡[71]	...	Mid point from end of QRS to end of T wave	...
Sayen et al.[72]	...	...	DC to ...
Maroko[73]	...	...	0.14 to 70

* Measurement criteria and amplifier frequency characteristics were obtained from a random search through more than 70 journal and textbook articles dealing with quantitative measurements of the TQ-ST segment deflection.

† Position along T-P or P-Q segments from which the diastolic end point was taken was seldom reported.

‡ Computer-assisted.

... = not reported.

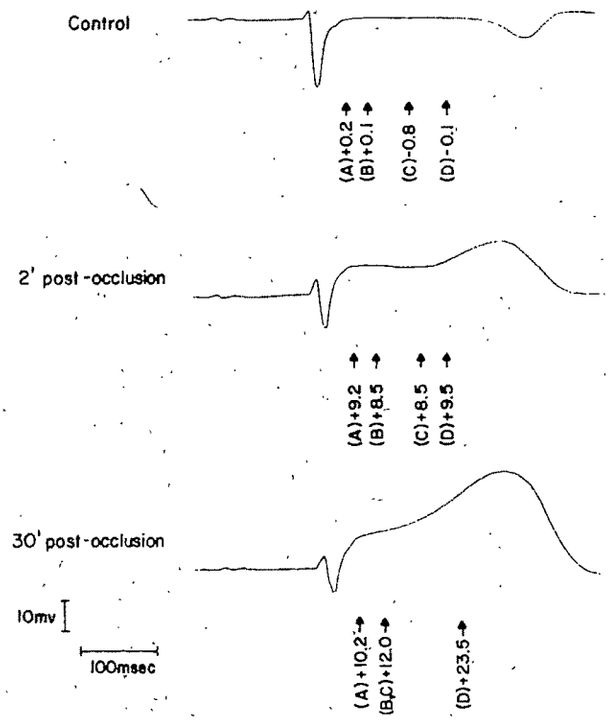


FIGURE 1. Comparison of various criteria used in the measurement of the TQ-ST segment deflection before and during acute coronary occlusion. The diastolic end point consisted of that portion of the T-Q segment occurring immediately before inscription of the QRS complex, and the systolic end point was either (A) the J point, (B) a point 60 msec after the nadir of the S wave, (C) the lowest point of the S-T segment when it is horizontal or the inflection point when it is not, or (D) the mid point between the end of the QRS complex and the end of the T wave. When the S-T segment rapidly slopes upward (30′ post-occlusion) the values so measured show considerable dispersion. Tracings illustrated are high speed epicardial electrograms.[76]

Firmly attaching atraumatic electrodes would seem to be the ideal choice. Usually constructed of polished metal and attached to the epicardial surface with a cyanoacrylate adhesive, these electrodes permit a fixed placement and continuous recording from multiple cardiac sites.[59,60] Tracings obtained with this type of electrode can be seen in Figure 1.

The recording amplifier and display system used are also important.[61] Generally all clinical and most experimental S-T mapping studies have used capacitor-coupled or alternating current amplifiers. Such amplifiers are used because they negate, over time, signal variations due to electrode-surface potentials (junctional potentials) that would otherwise introduce artifactual fluctuations into the baseline of the recordings. Use of capacitor-coupled amplifiers does not permit the separate analysis of the component T-Q and S-T segment deflections, only the total TQ-ST deflection. The frequency characteristics of such amplifiers and their display systems may vary, however (Table I). An amplifier or recorder with a poor low frequency response will attenuate and thus fail to reproduce faithfully the low frequency components of the electrogram—specifically the T-Q and S-T segment deflections. An amplifier with a poor high frequency response will not permit clear separation of high and low frequency components when it is required, as in the identification of the J point (see later).

Measurement of the TQ-ST Segment Deflection

The various criteria used in determining the diastolic and systolic end points of the TQ-ST deflection are listed in Table I. Theoretically, electrical diastole should comprise the entire T-Q segment and its components, the T-P and P-Q segments, and it should be horizontal and colinear. This is not always the case. For example, during periods of sinus tachycardia the P wave will be superimposed on the descending limb of the T wave and no true T-P segment will exist. The P-Q segment in turn may have superimposed upon it an atrial T wave. Generally the atrial T wave is either too small or falls completely within the QRS complex to be of significance in the measurement of the TQ-ST deflection.[74] When vagal influences predominate, atrial repolarization may be sufficiently shortened so that the atrial T wave will be inscribed shortly after the P wave, thus preventing the establishment of a well defined horizontal P-Q segment. Although deflections attributable to atrial activity are observed in precordial, esophageal and limb leads, they are at minimal, and often unrecognizable, levels in leads taken in or from most areas of the ventricular myocardium.

A proper characterization of the systolic end point of the TQ-ST segment deflection can be even more difficult to arrive at. The S-T segment, by definition (American Heart Association Committee on Electrocardiography[75]), is that portion between the end of the QRS complex (J point) and the upstroke or downstroke leading to the apex or nadir of the T wave. In many tracings the point or shoulder that marks the end of the QRS complex (J point) is followed by a nearly horizontal or gently sloping segment that eventually merges imperceptibly with the T wave. In such cases, measurements along any portion of the S-T segment yield comparable values. However, the segment is not always horizontal and may move toward the peak of the T wave immediately after completion of the QRS complex. In such cases the different sets of criteria in Table I are expected to yield values for the TQ-ST segment that show considerable dispersion. In addition, conditions that alter the position of the T wave (temperature and heart rate, for example) may then influence the degree of dispersion. This is shown in Figure 1, in which four criteria were used in the measurement of the TQ-ST segment deflection observed before and during acute coronary occlusion. The diastolic end point was the same for all and consisted of that portion of the T-Q segment occurring immediately before the inscription of the QRS complex. The systolic end point was either (A) the J point, (B) a point 60 msec after the nadir of the S wave, (C) the lowest point of the S-T segment when it is horizontal or the inflection point when it is not, or (D) the mid point between the end of the QRS complex and the end of the T wave. When the S-T segment was horizontal the values obtained according to any one set of criteria were comparable, although not necessarily identical, to one another. When the S-T segment rapidly sloped upward, the values obtained showed much greater dispersion.

Nomenclature

The terminology used to characterize the TQ-ST deflections in relation to the ischemic changes in the underlying tissue has not been standardized. Despite widespread references to the severity, extent, intensity, degree and magnitude of the ischemic process, these terms have no universally adopted definitions. More precise definitions should distinguish between the spatial and nonspatial characteristics of the ischemic process.[76] Spatial characteristics refer to the area of ischemic involvement (surface area of epicardium involved in the ischemic process) or ischemic size (mass of myocardium

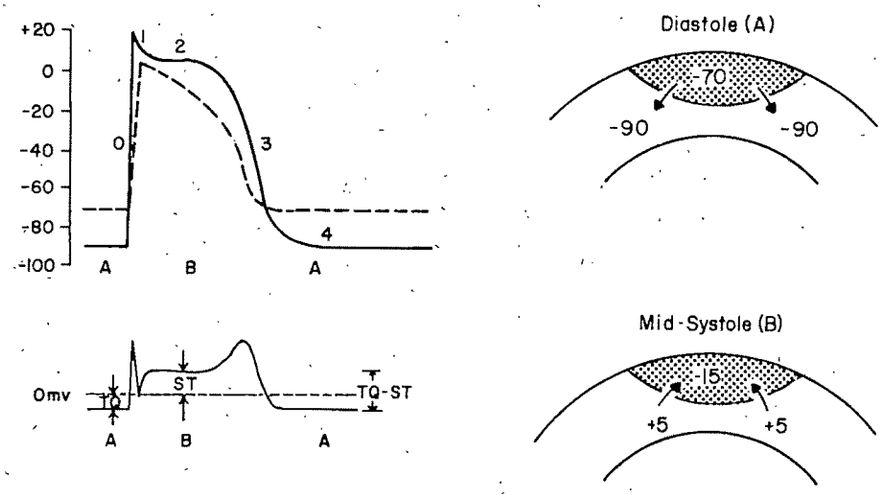


FIGURE 2. Top left, transmembrane potentials of ischemic **(broken curve)** and normal **(solid curve)** tissue. Numbers indicate phases 0 to 4. Phase 0 = initial rapid upstroke; phase 1 = phase of early rapid repolarization; phase 2 = plateau phase of slow repolarization; phase 3 = terminal phase of rapid repolarization; phase 4 = diastolic period. **Bottom left,** electrocardiogram recorded by an electrode overlying the ischemic tissue. The T-Q segment is located below the isoelectric line **(broken)** and the S-T segment above. **Top right,** potential gradients existing at the boundary between normal (−90 mv) and ischemic (−70 mv) tissue during electrical diastole. **Bottom right,** potential gradients existing at the boundary between normal (+5 mv) and ischemic (−15 mv) tissue at mid systole. **Arrows** indicate the direction of current flow (positive to negative) at the boundary.

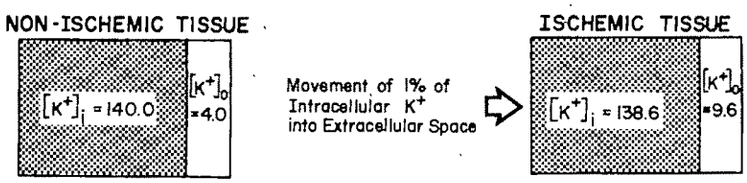
involved in the ischemic process); nonspatial characteristics refer to the rate at which different indications of injury become apparent whether they are metabolic (adenosine triphosphate [ATP] and creatine kinase [CK] depletion, potassium loss, decrease in oxygen tension and pH), hemodynamic (reduction in myocardial blood flow, decrease in developed tension), electrical (onset of conduction abnormalities and arrhythmias) or morphologic (mitochondrial swelling, clumping of chromatin).

Theoretical Considerations

Electrophysiologic events underlying the TQ-ST segment: The primary electrophysiologic events thought to be occurring in the underlying normal and ischemic myocardium are illustrated in Figure 2. During ischemia the transmembrane potential of the ischemic cells is altered as compared with normal cells. During diastole (phase 4) the ischemic cells have a lower resting transmembrane potential than normal cells[39,40,77,78]; as a result, current flows from the ischemic to the normal tissue.[79] During systole (phases 2 and 3) the transmembrane potentials of the ischemic cells become negative earlier than those of normal cells,[39,40,77,78,80,81] presumably because of either incomplete depolarization or early repolarization, or both,[40] reflected primarily in the shortening of phase 2 and decrease in action potential overshoot.[77] Now the potential gradient at the boundary between the two tissues is reversed and current flows in the opposite direction. The current flow during diastole causes the T-Q segment to be depressed in leads overlying the ischemic area. During systole the current flow is reversed and the S-T segment in the same leads is elevated. Thus the phenomenon commonly referred to as "S-T segment elevation" is believed to be the sum of T-Q depression and S-T elevation.[38–40,57,69,82] The relative contribution of each of these diastolic and systolic components to the total deflection has not yet been clearly established[35,39,57,78] and may be time-dependent.[39,40] Therefore the TQ-ST segment deflection seen in the electrogram depends primarily upon the potential differences and subsequent current flow arising at the boundary between the normal and ischemic tissues. If these differences disappear, then so also must the TQ-ST deflection.[9,83]

Mechanism of ischemic changes in the transmembrane potential: Any theory attempting to identify the agent or event accompanying the cessation of flow that is most likely responsible for the early alterations in the transmembrane potentials of the ischemic cells must successfully account for the following experimental observations. First, the agent must alter the potentials during diastole as well as systole.[38–40,57] Second, the alterations must occur extremely rapidly in order for TQ-ST segment deflections to be observed within seconds after cessation of flow.[35,69,72,76] Of the many changes known to occur in tissue after the onset of ischemia,[84] only four appear to be capable of significantly influencing the action potential. These include a reduction in oxygen tension, deprivation of substrate, reduction in pH and the extracellular accumulation of potassium (K^+). The latter meets all the requirements listed. Although a decrease in oxygen tension occurs rapidly enough,[72] its influence on the action potential consists primarily of a shortening of action potential duration requiring several minutes to become noticeable.[80,85] Similar findings are seen after the deprivation of substrate (glucose, for example) or the administration of a metabolic inhibitor.[86,87] A decrease in pH, while occurring rapidly,[88] has only a minor effect on the action potential and this is again limited to systole.[89] The combined effect of two or more of these factors (for example, hyperkalemia and anoxia, decreased pH and lack of substrate) on the transmembrane potential has not yet been examined.

Extracellular accumulation of K^+ (efflux of intracellular K^+): The evidence implicating potassium is substantial[33,83,90–95] although not conclusive (see Addendum A). In addition to the repeated observations that either topical application to the heart's surface[33] or the intracoronary infusion of a hyperkalemic solution[95] evokes TQ-ST segment deflections that are similar to the deflections observed during ischemia as well as the reported correlations between the magnitude



$[K^+]_i / [K^+]_o$	35.0	14.4
E_k (mv)	95.1	71.1
APD (msec)	260	145

FIGURE 3. Computed effect of an ischemia-induced 1 percent loss in intracellular **(shaded)** potassium (K^+) into the extracellular space on equilibrium transmembrane potential (E_K) and action potential duration (APD). E_K calculated from the Nernst equation at 37° C and APD derived from observations of Surawicz.[96] Extracellular space was assumed equal to 20 percent of total tissue volume.[97] Intracellular and extracellular potassium concentrations denoted by $[K^+]_i$ and $[K^+]_o$, respectively.

of the TQ-ST deflection and coronary sinus potassium concentrations during ischemia,[93] calculations by Johnson[37] indicate that with active K^+ influx, arrested passive efflux of K^+ would be capable of raising the extracellular K^+ concentration from 5 to 10 millimolar in only 10 seconds. As illustrated in Figure 3, as little as a 1 percent loss of intracellular K^+ into the surrounding extracellular space will increase the concentration here by 140 percent. With use of the Nernst equation and data from Surawicz[96] and Polimeni,[97] it can be calculated that this should result in a significant lowering of the resting membrane potential and reduction of action potential duration. If coronary flow is not completely absent or if other mechanisms facilitate the removal of the leaked K^+ (see later), then more rapid or greater K^+ losses are required before the extracellular K^+ level in the ischemic tissue begins to rise.

The mechanism by which this initiation of K^+ leakage may be effected is unknown, but at least two possibilities exist. The first hypothesis assumes that ischemia rapidly arrests the sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) pump and its coupled transport of K^+ into the cell.[37] Normal K^+ efflux continues, however, eventually accumulating in amounts sufficient to alter the membrane potential of the ischemic cell. The second hypothesis suggests that very early in ischemia the Na^+-K^+ ATPase pump is not inhibited but that ischemia somehow brings about a sudden increase in the potassium permeability of the cell, thereby accelerating the efflux of K^+ from the cell. Eventually the Na^+-K^+ pump is overloaded, thereby permitting the extracellular accumulation of K^+ (see Addendum B).

Magnitude and polarity of TQ-ST deflection: Once a source of current has been established by the potential gradient existing at the boundary of the normal and ischemic segments, the magnitude and polarity of the TQ-ST deflection are determined by the orientation of the recording electrode with respect to this boundary, the spatial geometry of the ischemic region and the nature and extent of the conductor with which both the electrode and the heart are in contact.[79,98] Expressions relating the TQ-ST deflection to these factors may be derived by quantitative application of the solid angle theorem,[69,83,99] a mathematical statement that relates the potential recorded at an electrode site to the flow of currents in homogeneous volume conductors of infinite extent.[31–33,69,98,100] The fact that

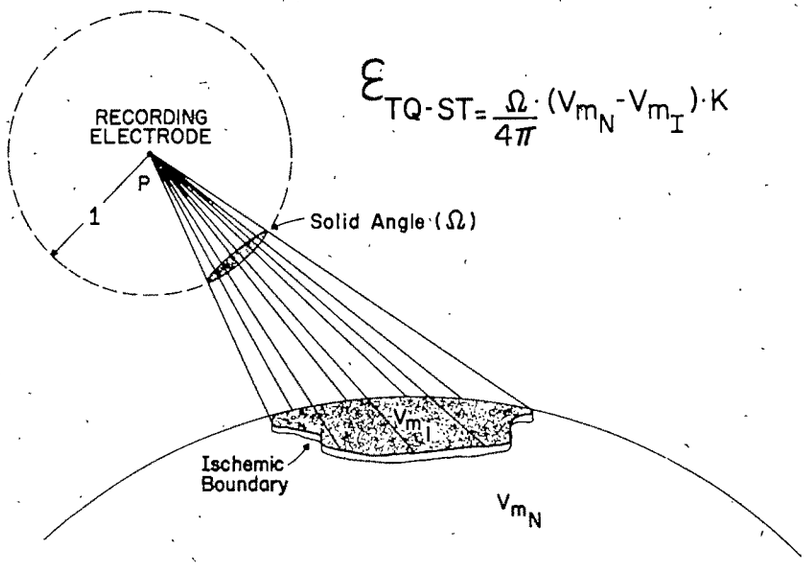


FIGURE 4. Mathematical and pictorial characterization of the solid angle theory. The TQ-ST segment voltage recorded at the electrode is given by the equation. The solid angle Ω is defined as the area of spherical surface cut off a unit sphere (inscribed about the recording electrode) by a cone formed by straight lines extending between the recording electrode and every point along the ischemic boundary. The ischemic boundary is a source of current flow established by differences in the transmembrane potentials of the normal (V_{m_N}) and ischemic (V_{m_I}) cells during diastole and systole. K is a term correcting for differences in intra- and extracellular conductivity and the occupancy of much of the heart muscle by interstitial tissue and space.

$$\mathcal{E}_{TQ\text{-}ST} = \frac{\Omega}{4\pi} \cdot K \cdot (V_{m_N} - V_{m_I})$$

SPATIAL NON SPATIAL

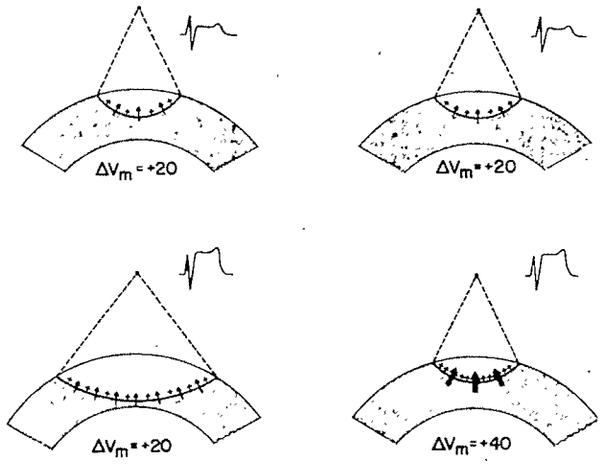


FIGURE 5. Comparison of spatial **(left)** and nonspatial **(right)** influences on the ischemic TQ-ST segment deflection. In the example at the left, the solid angle subtending the boundary increases with an increase in ischemic area as does the TQ-ST segment deflection. In the example at the right, the electrode location, ischemic area and the solid angle remain constant; however, the difference in transmembrane voltages between the two regions during systole (ΔV_m) has widened and the current flow intensified **(heavy arrows).** As a result, the TQ-ST segment voltage again increases; however, this time the extent of the ischemic process has not changed.

TABLE II

Factors Influencing TQ-ST Deflection During Myocardial Ischemia

I. Spatial factors
  A. Electrode location[33,34,69,83]
    1. Precordial, epicardial, endocardial, intramyocardial or intracoronary
    2. Centrally or peripherally situated over ischemic/non-ischemic area
  B. Ischemia
    1. Area of ischemic involvement[4,9,69,83,99,103]
      a. Single areas
      b. Multiple areas[4]
    2. Wall thickness[54,79]
      a. right versus left ventricle
      b. base versus apex
    3. Heart size
    4. Shape of ischemic involvement[33,34,69,83,104,105]
      a. subepicardial, transmural, subendocardial
      b. intramural isolation
  C. Infarction[106,107]
II. Nonspatial factors
  A. Transmembrane potential in normal or ischemic areas, or both (Table III)
  B. Potassium balance in the myocardial cell (Table IV)
  C. Potassium removal from the ischemic area
    1. Tissue diffusion factors[108]
    2. Collateral blood flow[109]
    3. Venous drainage[110]
    4. Lymphatic drainage[111]
    5. Coronary reperfusion[112]
  D. Ventricular arrhythmias and conduction disturbances[4,113–115]
    1. Bundle-branch block
    2. Ventricular tachycardia
    3. Peri-infarction block
III. Pre-existing TQ-ST segment deflections
  A. Digitalis therapy[116,117]
  B. Pericarditis[118]
  C. Ventricular aneurysm[119,120]
  D. Cardiomyopathy[121]
  E. Central nervous system disease[122]
  F. Pacemaker-induced[123]
  G. Atrial repolarization[74]
  H. Early repolarization[124]
  I. Electrode artifact

the thorax is of finite proportions and consists of regions of varying conductivity does not appear to limit the theorem's usefulness in evaluating TQ-ST segment phenomena.[31,69,83,101] A review of the advantages and limitations of solid angle analysis in electrocardiographic interpretation has recently been written.[102]

The magnitude and polarity of the TQ-ST segment voltage recorded at an electrode site P is equal to the product of three parameters (Fig. 4): Ω is the solid angle subtended at P by the ischemic boundary; V_{m_N} and V_{m_I} denote the transmembrane potentials of the normal and ischemic regions; and K is a term correcting for differences in intra- and extracellular conductivity and that portion of the heart muscle occupied by interstitial tissue and space.[100] Because the solid angle depends only upon the position of the recording electrode and the geometry of the ischemic boundary, it reflects *spatial* influences on the magnitude of the TQ-ST deflection. However, the difference in transmembrane potential between the two regions does not depend upon geometry and thus this difference reflects *nonspatial* influences on the TQ-ST deflection.

This distinction between spatial and nonspatial factors is important. In Figure 5, the relative magnitude and direction of current flow from the normal to the ischemic region during systole are indicated by arrows. On the left, a spatial influence is shown. With a precordial electrode, the solid angle is observed to increase after an increase in ischemic area and, according to the equation, the voltage of the TQ-ST deflection must also increase. On the right, a nonspatial influence is depicted. In this case, electrode location, ischemic area and the solid angle remain constant, but the transmembrane potential difference, ΔV_m, between the two regions has widened and the current flow has intensified. The TQ-ST deflection voltage is again increased but the extent of the ischemic process is not altered. The magnitude of the TQ-ST segment deflection is also determined by the tissue conductivity term K. Whether or not this latter variable changes significantly during ischemia has not been studied (see Addendum C).

Factors Influencing the TQ-ST Segment Deflection During Ischemia

TQ-ST segment deflections recorded during ischemia are influenced by spatial, nonspatial and other factors (Table II).

Spatial Factors

Electrode location and the area of ischemic involvement: Spatial factors that affect the TQ-ST de-

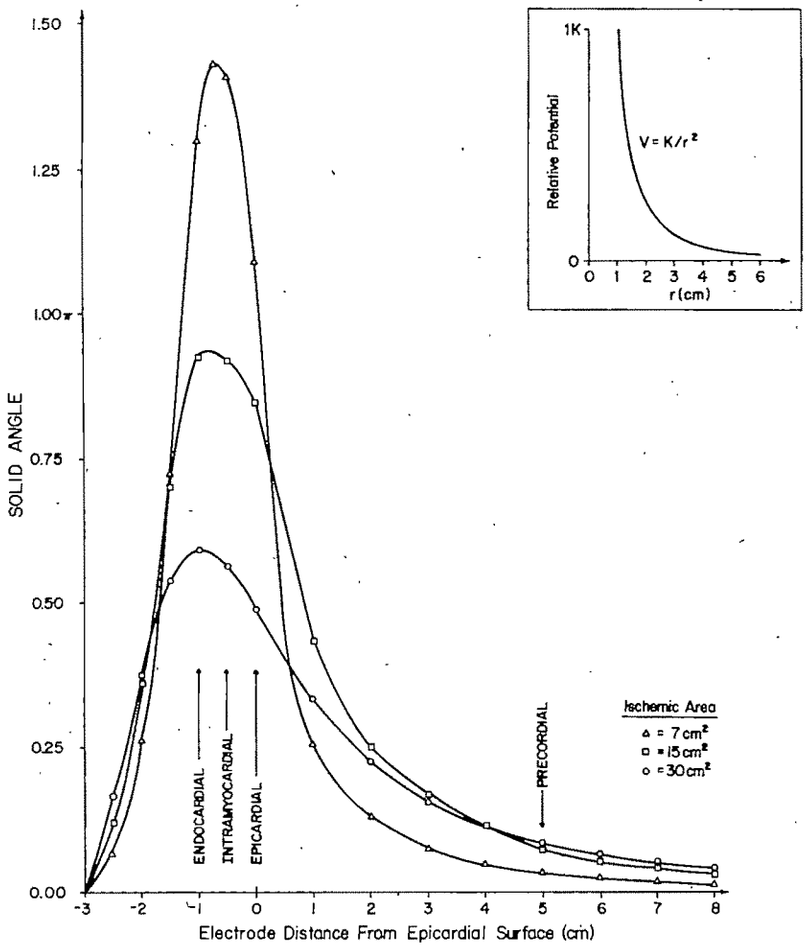


FIGURE 6. Effect of electrode location and area of ischemic involvement on magnitude of the solid angle. Curves were derived from quantitative application of the solid angle theorem[98] to a spherical model of the left ventricle containing a well defined ischemic region.[69,83] The relation between solid angle magnitude and electrode location begins to be parallel to that of the classic potential curve as the electrode is moved farther away from the heart's surface **(Inset).** At an epicardial, intramyocardial or endocardial location, increases in ischemic area result in decreases in the solid angle.

flection do so by altering either ischemic geometry or electrode location.[34,83,102] As shown in Figure 6, with an electrode at the relatively distant precordial position, increases in ischemic area increase the solid angle values and therefore the magnitude of the deflection. However, because of their relative proximity to the ischemic boundaries, at epicardial, intramyocardial or endocardial locations the situation is reversed and increases in ischemic area result in *decreases* in the solid angle and the TQ-ST segment deflection. Experimental confirmation of these predicted differences with respect to changes in ischemic area at epicardial[69,83,99] and precordial[69,103] locations has been made in both the dog[99] and the pig.[69,83,103]

Multiple ischemic areas: To describe accurately the relation between the TQ-ST deflection and multiple ischemic areas, the solid angles constructed by each area must be individually computed and then summed together.[98] It can therefore be appreciated that (1) the TQ-ST deflection recorded from two or more areas of involvement is *not* equal to that recorded from a single large area totaling the sum of the smaller areas, and (2) two unequal areas of ischemic involvement located at opposite sites in either the ventricular wall (subepicardial versus subendocardial) or in the heart (anterior versus inferior wall) may have a resultant TQ-ST deflection approaching zero.[9,98]

Wall thickness and heart size: Changes in wall thickness and heart size are also expected to influence the magnitude of the TQ-ST deflection and should be considered before other less specific mechanisms.[83] For example, differences in wall thickness known to exist between the right and left ventricles or the base and apex of the left ventricle may account for differences in the TQ-ST deflections recorded from these areas.[54,83] Analysis of potential deflections recorded with multiple epicardial electrodes demonstrated the existence of at least six anatomically and statistically identifiable TQ-ST deflection populations (Fig. 7). Given only the geometry of the anteroseptal ischemic region and the positions of the recording electrodes, one may calculate a similar potential distribution directly from the solid angle theory (Fig. 7, top right). Although criteria at the epicardium for an "ischemic site" vary considerably,[50,56,58,125] it would appear on the basis of these data that sites either not overlying the ischemic region (right ventricular nonischemic) or overlying it partially (border) or completely (right ventricular ischemic) might be difficult to categorize simply on the basis of polarity and voltage criteria.

Ischemic shape: Changes in ischemic shape may also influence the magnitude and specifically the polarity of the TQ-ST segment deflection.[33,34,69,104,105] Currently it is difficult to predict or detail such changes in either

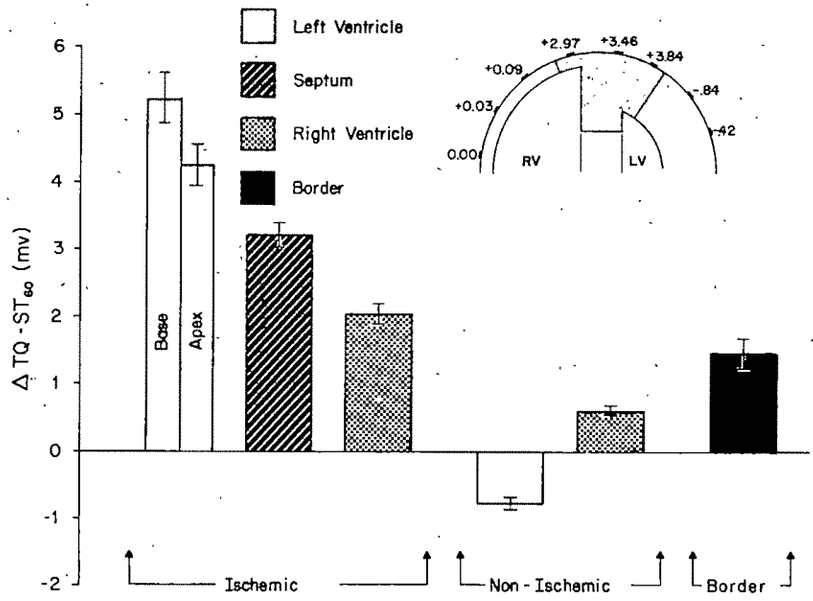


FIGURE 7. Populations of TQ-ST segment deflections recorded from multiple epicardial electrodes (radius = 2.2 mm) attached to the heart's surface during 77 very brief occlusions of the distal one third of the left anterior descending coronary artery in 17 pigs. Electrodes were evenly spaced over the anteroseptal portion of the heart and categorized on the basis of anatomic location. Septal sites were within 0.5 cm of the main trunk of the left anterior descending coronary artery, and border sites (right [RV] and left ventricle [LV]) overlay both normal and cyanotic tissue. $\Delta TQ\text{-}ST_{60}$ = change from control in measured TQ-ST segment magnitude at 60 seconds after occlusion. Electrograms were randomly coded and evaluated without prior knowledge of electrode location. Values are expressed as mean ± standard error of the mean and all *P* values obtained from paired *t* test comparison of any two potential populations are less than 0.002. Ischemic area as estimated from area of cyanotic discoloration was 13.2 ± 0.8 cm^2. Data adapted from Holland et al.[83]

a clinical or an experimental situation. Differences in ischemic shape do occur, however, and their expected effects on the TQ-ST deflection can also be predicted with use of solid angle theory.[69] As illustrated in Figure 8, ischemic involvement of only the outer portion of the ventricular wall should yield positive TQ-ST deflections of maximal magnitude at either precordial or epicardial locations. In contrast, ischemic regions localized to the inner portion of the wall yield negative deflections in overlying leads.[34] Finally, ischemic segments of the ventricular wall that are isolated in the middle of the wall and extend neither to the epicardial nor the endocardial surfaces will appear to be electrically silent in both the precordial and epicardial leads.[34,104] However, if intramyocardial electrodes are placed within the ischemic region, TQ-ST segment deflections should theoretically be recorded.[83] If one recognizes that patchy intramural ischemic regions are often seen in the dog,[127] the observation made in this species that intramyocardial electrodes are more sensitive indicators of ischemia than epicardial electrodes[72,128] is not surprising. In summarizing their classic study on the influence of ischemic shape on the polarity of the TQ-ST deflection, Hellerstein and Katz[34] stated: "We have shown that the direction of the S-T displacement depended purely upon the spatial orientation of the exploring electrode in relation to the theoretical surface (boundary) between injured and uninjured areas . . ."

Electrode positions overlying ischemic and nonischemic regions: The curves of Figure 6 were determined for electrodes directly overlying the ischemic regions. However, in most mapping studies, electrograms are recorded from peripheral portions of the ischemic region and from the ischemic border and nonischemic sites (Fig. 7) as well. Solid angle descriptions of TQ-ST segment behavior are equally valid at these locations. When the ischemic boundary is sharp and well defined and the wall thickness of the ischemic segment is assumed to be constant, the calculated

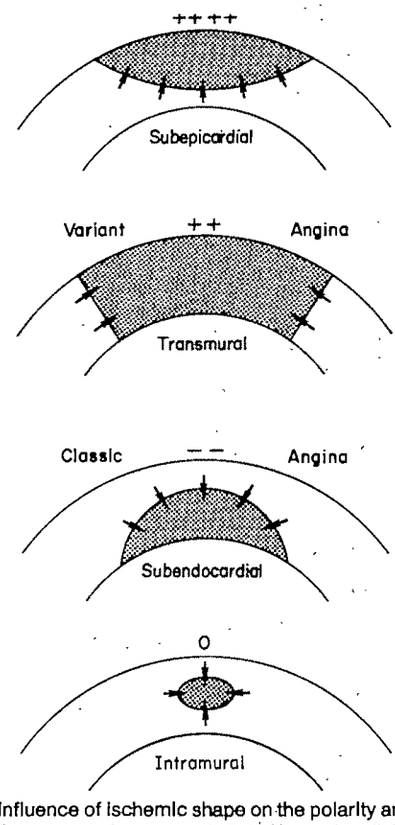


FIGURE 8. Influence of ischemic shape on the polarity and magnitude of the TQ-ST segment voltage recorded at either epicardial or precordial locations. The direction of current flow during systole at the ischemic boundary is indicated by **arrows.** Subepicardial ischemia in which only the outer portion of the ventricle wall is involved yields positive deflections of maximal magnitudes. With subendocardial ischemia the direction of current flow is away from the electrode and negative deflections are observed in overlying leads. Ischemic segments that are isolated in the ventricular wall are electrically silent.[34,98,104] This figure also suggests that the differences in the polarity of the TQ-ST segment deflections seen with Prinzmetal's variant angina, in which the TQ-ST segment is elevated and in classic angina, in which it is depressed, are largely due to differences in ischemic shape.[124]

TQ-ST segment deflection at epicardial sites is relatively constant over the ischemic region with a small increase in its magnitude predicted for sites close to the ischemic boundary.[83] In the pig,[109,129] baboon[130,131] and normal human being[132] there are few functionally significant collateral vessels, and therefore one expects the ischemic boundary to be well defined.[133] However, in the dog, with its richer collateral blood supply,[109] evidence suggests that the border lacks such definition,[134] and thus a wide gradient of transmembrane potentials most likely exists at the periphery of the ischemic region.[98] In this instance, solid angle analysis predicts that maximal TQ-ST deflections should be recorded at the ischemic center, decreasing in magnitude as the ischemic boundary is approached. Data reflecting this difference in the magnitudes of the TQ-ST segments at central and peripheral ischemic locations between animals with (pig, baboon) and without (dog) a well defined boundary is rather sparse.[57,83,95] At the precordium, whether or not the boundary is well defined has little effect on the TQ-ST segment potential distribution.[83] Here theoretical[83] and experimental[4,52] evidence suggests that maximal deflections are recorded from sites directly overlying the ischemic center. The additional influence of wall thickness, ischemic shape, heart size and distance from precordium to heart may alter these distributions significantly (Fig. 7).[65,83]

Infarction: The clinical electrocardiograms from patients with acute myocardial infarction are usually taken within hours to days after the coronary occlusive event. By this time some cell death presumably has taken place and thus the electrogram reflects electrical changes due to *two* processes occurring in the myocardium: ischemia *and* infarction. The possible modification of the TQ-ST segment deflection by the latter process has, for the most part, not been investigated. As an example, the often dramatic fluctuations observed in the magnitude of the TQ-ST segment deflections during the first hours after acute coronary occlusion[6,8,10,36,135] may be due to steadily progressive electrical, biochemical and structural dysfunction of the cell culminating in necrosis (see Addendum C). Although the transmembrane potential abnormalities recorded during early ischemia (0 to 20 minutes) may be reasonably attributed to the effects of local potassium accumulation, the mechanism of changes seen with chronically ischemic, infarcted or fibrotic tissue has not yet been elucidated. In the study of Ten Eick et al.,[106] in which the posterior papillary muscles of dogs with a 60 minute circumflex arterial occlusion were placed in a tissue bath (K^+ = 4.0 millimolar), abnormalities recorded included partial depolarization of resting potential, lengthening *and* shortening of action potential duration, altered relation between action potential duration and cycle length, reduction in upstroke velocity and membrane responsiveness and oscillatory phenomena. Similar findings were reported by Myerburg et al.[107] in a study of chronic myocardial infarction in cats and by Amat-y-Leon et al.[136] in diseased atrial tissue. The ultimate effect of such changes in transmembrane potential on the TQ-ST segment deflection will be determined by the location and distribution of cells in the injured region that manifest such abnormalities.

The possibility that the complete loss of electrical activity, as seen with cell death, might play some role in modifying the TQ-ST segment deflection was contemplated by Wilson et al.[1,31] and Bayley[32] more than 30 years ago. Although ischemic cells, which are electrotonically coupled to one another and to normal cells, may conduct ionic currents intercellularly, dead cells are not coupled and therefore behave as part of the extracardiac volume conductor, that is, in a fashion similar to that of other thoracic structures (such as blood, bone, skeletal muscle, lung)[98] (see Addendum C). Because theory suggests that it is current flow at the boundary of the normal and ischemic tissue from which the TQ-ST segment deflection arises, persistence of the deflection in the days to weeks after the initial occlusive event may actually reflect electrical activity only at the boundary where a population of ischemic cells exists, and not in the center of the injured region where many of the cells may already have died and are therefore electrically silent. If this situation exists, then pharmacologic manipulation of the TQ-ST segment deflection in patients with acute myocardial infarction may represent changes in the electrical activity of a theoretically very small thickness (for example, a few cell layers) of ischemic tissue.[8] More importantly, if after this intervention this tissue *either* regains electrical normality *or* dies, improvement (such as reduction

TABLE III

Factors Directly Influencing the Transmembrane Potential in Normal or Ischemic Areas, or Both

	Resting Membrane Potential	Action Potential Duration
Metabolic		
Anoxia[80,85]	NC	↓
Ischemia[39,40,77]	↓	↓
Dinitrophenol[86]	NC	↓
Glucose[87]	NC	NC†
Electrolytes		
Hyperkalemia[137,138]	↓	↓
Hypercalcemia[139]	NC	↓ ‡
Antiarrhythmic agents		
Propranolol[40,140]	↓ (high dose)	NC†
Quinidine[138,141]	NC	↑
Lidocaine[141]	NC	NC†
Bretylium[142]	NC	↑
Diphenylhydantoin[143,144]	NC*	NC
Inotropy		
Ouabain[145,146]	NC	↓
Catecholamines[147]	NC*	NC
Chronotropy[148]*	NC	↓
Psychotropic agents		
Phenothiazine[149]	NC	↑
Imipramine[150]	↓ (high dose)	↑
Hypothermia[151,152]	NC	↑

*Resting membrane potential of partially depolarized cells returned to more normal levels.[143,144,153]

†Action potential duration of ischemic/anoxic cells returned to more normal values.[40,154,155]

‡K^+- and pH-dependent.

NC = no change.

in amplitude) of the TQ-ST segment deflection should occur.[9]

Nonspatial Factors (Intervention Factors)

Mechanism by which a given intervention alters the magnitude of the TQ-ST segment deflection: It is often presumed that observed changes in TQ-ST deflection during an intervention reflect concomitant changes in the severity and extent of the ischemic process. Theory and experiment indicate that such an assumption may be incorrect under a variety of conditions. As discussed earlier (see "Theoretical Considerations" and Fig. 2, 4 and 5), the TQ-ST segment deflection is a function not only of electrode location and ischemic geometry (spatial influences), but also of the difference in transmembrane voltage (ΔV_m) between ischemic and normal tissues during both systole and diastole (nonspatial influences). Changes in ΔV_m will be reflected in corresponding changes in TQ-ST segment voltage (equation, Fig. 4). The list of agents potentially capable of altering ΔV_m is large and diverse. These agents may be placed in one or both of two categories. An agent may be expected to change ΔV_m by (1) directly altering the transmembrane potentials of either the *normal* or the *ischemic* cells (Table III), or (2) influencing the rate and degree of potassium accumulation in the extracellular space of the ischemic tissue. The latter may be accomplished by either altering the rate of K^+ leakage out of the ischemic cells (Table IV) or altering the rate of its removal from the extracellular space of the ischemic tissue. Emphasis placed here on interventions that modify K^+ leakage assumes that K^+ accumulation is an important, if not the primary, mechanism responsible for the genesis of the ischemic TQ-ST segment deflection (see "Theoretical Considerations" and Addendum A).

Experimental findings also suggest that both nonspatial and spatial factors determine the magnitude of the TQ-ST deflection. Consider the following: (1) The TQ-ST segment magnitude increases with increases in the area of ischemic involvement when the electrogram is recorded from the precordium, but decreases when the electrogram is recorded from the epicardium[69,83,99,103]. (2) The TQ-ST segment magnitude increases after infusion of isoproterenol and decreases with administration of propranolol or potassium irrespective of electrode location or ischemic size.[4,50,51,58,83,195,196] It follows then that changes observed in the TQ-ST deflection in the latter example cannot always be accounted for on the basis of spatial influences (electrode location and ischemic size), although such changes may indeed have occurred.

We are not in any way suggesting that propranolol or any other agent cannot modify the oxygen demands and supply of the ischemic segment and thereby modify eventual infarct size. Rather we are proposing the possibility that *the mechanism by which an agent influences the TQ-ST segment may be unrelated to its ability (or lack of it) to effect changes in the geometry (size) or function (tension development, lactate production) of the ischemic segment.* In those experimental animal studies in which tissue CK and histologic examinations are used to delineate the extent of the infarcted region, a number of agents have been shown to have an efficacious or detrimental effect on eventual infarct size.[3] However, in clinical situations in which these same or different agents are studied, these rather specific methods can no longer be used. If, then, TQ-ST segment mapping is employed as the primary means of assessing the injured area,[197] it becomes necessary to determine just how specific and sensitive an indicator of injury we can expect it to be. In the following pages, then, we will first discuss mechanisms by which an agent may influence the TQ-ST segment without necessarily either modifying infarct size or improving the function of the injured region and then examine the degree to which mapping correlates with alternate measures of the ischemic process.

Factors directly influencing the transmembrane potential: Most agents capable of altering the ventricular action potential in normal cells (Table IV) do so by shortening or lengthening its duration and thus might be expected to exert their influence on the S-T segment half of the ischemic electrogram. If, for example, ouabain shortens the action potential duration of nonischemic and ischemic cells by the same degree, then the preexisting potential differences of the two areas are maintained and the magnitude of the TQ-ST deflection may be left unaltered by ouabain's presence. If, however, the action potential duration of the nonischemic cells experiences a greater degree of shortening, these cells, although still healthy, will begin to mimic, in part, the action potential shape of the ischemic cells. The potential differences previously existing during systole between the two tissues will diminish and the S-T por-

TABLE IV

Factors Influencing Potassium Balance in the Myocardial Cell

Increased Potassium Loss	Decreased Potassium Loss
Inotropy[156,157]	Antiarrhythmic agents
Calcium[158]	Propranolol[76,180]
Ouabain[159]	Quinidine[180]
Catecholamines*[160,161]	Procainamide[181]
Paired stimulation[162]	Lidocaine[182]
Chronotropy[163–166]	Potassium
Preload[167]	Potassium salts[183]
Afterload[168]	K^+-Hyaluronidase[184]
Hyperthermia[169]	K^+, Mg^{++}-Aspartate[185]
Metabolic	Acetylcholine[186]
ATP inhibition[87]	Hypothermia[169,187]
Anoxia/ischemia[90,170]	Metabolic
Acidosis[169,171,172]	Insulin[188]
Adrenalcorticoids†	Glucose[87]
Cortisone[173]	Taurine[189]
Aldosterone[174]	Hypoxia[190]
Deoxycorticosterone[175,176]	Alkalosis[191]
Fluorocortisone[177]	Diuretic drugs
Diuretic drugs	Spironolactone[178,179]
Furosemide[178]	Triamterene[178,179]
Ethacrynic acid[178,179]	Amiloride[192]

*In addition to rate-dependent changes.

†Losses may be due to either direct hormonal action on myocardial K^+ metabolism or renal K^+ excretion.[193,194]

tion (and thus the total TQ-ST deflection) will decrease in magnitude. Conversely, if the ischemic tissue experiences the greater degree of shortening, then the opposite will occur and the TQ-ST deflection should increase.

Recent studies indicate that the electrophysiologic actions of an agent on the transmembrane potential of a cell are clearly dependent upon whether or not the cell is ischemic.[40,143,144,153–155] Catecholamines, while having no effect on resting transmembrane potentials of normal cells, tend to restore the potential toward normal in partially depolarized (for example, ischemic) cells.[153] The selective influence of propranolol[40,154] and lidocaine[155] on ischemic cells has also been studied. Kupersmith et al.[154] observed that during control coronary arterial ligation in dogs the action potential duration in the ischemic zone was 25 msec shorter than in the normal zone. After administration of 40 μg/kg of propranolol this difference was obliterated. Similar results were reported with lidocaine.[155] The factors postulated to account for this selective action[154,155] may include the lower pH, higher extracellular potassium, local accumulation of metabolic byproducts or merely the different action potential configuration characteristics of the ischemic segment. Since the S-T segment component of the total TQ-ST segment deflection is believed to arise from a disparity in action potential magnitude and duration between normal and ischemic cells, the reduction in TQ-ST elevation noted after administration of propranolol in both animals[4,50,51,58,83,195] and patients[196] could reasonably be attributed to its electrophysiologic actions on ischemic cells.[102] All in all it would then seem presumptuous to conclude that a given pharmacologic agent modified ischemic TQ-ST elevations solely by modifying the energy demands of the ischemic segment without first establishing that no direct electropharmacologic alterations in the ischemic (or normal) transmembrane potential had also occurred.

Factors influencing potassium balance in the ischemic tissue: The difficulty encountered in trying to resolve the problem just mentioned is compounded by the observation that many agents that *do* alter the energy demands of the heart in turn alter the potassium balance of the ischemic segment (Table IV). Such changes brought about in extracellular potassium concentration will then be capable of directly altering the transmembrane potential of the ischemic cells and hence the magnitude of the TQ-ST segment deflection. Changes in ischemic geometry that may also be effected by some of these agents—as discussed earlier—appear to be either insufficient in degree or occur in a direction opposite to that required to account entirely for the changes they elicit in the TQ-ST deflection.

A hypothesis suggesting that agents that modify energy demands in the ischemic tissue will also modify potassium balance in the ischemic tissue was arrived at by considering the following: (1) Previous experiments have demonstrated that uptake of potassium ions by excitable cells is closely coupled with the active extrusion of sodium ions. This active pumping of Na^+ ions out and coupled transport of K^+ ions into the cell requires the participation of high energy phosphate compounds (ATP). Inhibitors of either the Na^+-K^+ transport mechanism (ouabain) or of the formation of the ATP required for operation of the pump (cyanide, 2,4-dinitrophenol, ischemia) bring about a rapid block of sodium efflux while permitting the passive efflux of potassium to continue.[198,199] (2) After sudden increases in cardiac activity (either inotropic or chronotropic) in the normal heart, increases in both myocardial influx and efflux of potassium are observed.[154,164] However, if cardiac activity in the ischemic heart is increased, the production of ATP required for maintenance of even normal K^+ influx is decreased and K^+ efflux not only continues but is accelerated by the increase in activity.[165] Under such conditions, both extracellular accumulation of potassium and the magnitude of the ischemic TQ-ST deflection may increase.[163] (3) Conversely, decreases in K^+ loss and in the magnitude of the TQ-ST deflection may be due to decreases of fluxes in both directions or of efflux alone, or by possible enhancement of influx. Reported decreases in K^+ loss from ischemic tissue after metabolic intervention do not necessarily have to be attributed to stimulation of glycolysis and subsequent renewed or enhanced uptake of K^+ into the injured cell. Although this is probably the manner by which glucose maintains glycolytic flux and normal membrane potentials in the ischemic cell,[87] insulin (besides having important glucose transport functions) may also directly decrease potassium efflux.[188] Finally, potassium may stimulate K^+ uptake.[137,169,183] Thus the mechanism by which glucose-insulin-potassium reverses or limits the ischemic TQ-ST changes in the electrogram[200] may or may not be entirely due to suspected improvement in glycolytic flux and anaerobic ATP production effected by this regimen. (4) Sarnoff et al.[156] suggested that the relation between increases in cardiac activity and increased potassium leakage from the ischemic cell appears to be a general one; that is, hemodynamic interventions that bring about increases in oxygen consumption almost invariably increase the potassium fluxes across the myocardial cell.[156,157] However, the converse is not always the case. Adrenal corticosteroids and diuretic agents may also be capable of either increasing or decreasing potassium leakage out of the ischemic cell without increasing the oxygen demands of the cell. Ethacrynic acid, for instance, potentiates the digitalis-induced increase in the cardiac arteriovenous difference, whereas amiloride and spironolactone antagonize this effect.[179] The mechanism by which this occurs is not clear. This postulated link between oxygen consumption in ischemic tissue, potassium loss and the TQ-ST segment deflection may account for the observation that factors that increase myocardial oxygen consumption (for example, tachycardia, isoproterenol, glucagon, ouabain) often increase the amplitude of the TQ-ST deflection.[50] Whether this increase in potassium leakage also accounts for or reflects the reported detrimental influence of these same interventions on eventual infarct size[3] must await further study.

The observation that potassium may directly alter the transmembrane potential of the myocardial cell[138] and influence potassium balance in the ischemic tissue[137,183] suggested that potassium should have a particularly potent nonspatial influence on the TQ-ST segment deflection. As illustrated in Figure 9, TQ-ST segment deflections recorded from both the ischemic and nonischemic regions decreased with steadily increasing plasma potassium levels.[83] That the decline was logarithmic is interesting because both the potassium equilibrium E_K and the action potential duration, which correspond to the T-Q and S-T segments of the electrocardiogram, are log functions of K^+ over the range of 2.0 to 10 millimolar.[83,96]

This finding suggests that (1) increases in the TQ-ST segment deflection in the course of acute myocardial infarction may occur as a result of acute potassium depletion as seen following diuretic therapy, loss of gastrointestinal fluids, osmotic diuresis, adrenal hyperactivity, or nephritis; conversely, (2) TQ-ST segment deflections signifying injury may be absent in the presence of hyperkalemia due to acute renal failure.[201,202]

Potassium removal from the ischemic area: Potassium accumulation in the extracellular space of the ischemic tissue is the net result of potassium leakage out of the injured cell and its removal by one or more mechanisms from the ischemic region. Those mechanisms will include diffusion,[108] available collateral blood flow[109] and venous[110] and lymphatic drainage.[111] The rate-limiting step characterizing potassium removal is not known; however, a few points are worth considering. For instance, for coronary collateral flow to bring about a significant reduction in the TQ-ST deflection, it need not necessarily be so great as to sustain the oxygen requirements of the tissue, thereby reversing the ischemia, but perhaps only great enough to *wash out* the accumulating K from the ischemic tissue and into the peripheral circulation. Similarly, hyaluronidase by presumably altering interstitial permeability factors[202] again need only speed up K^+ removal to bring about an electrocardiographic improvement; significant oxygen and substrate delivery to the ischemic tissue, although desirable, may not be necessary for this effect. This washout phenomenon has been demonstrated both by Ekmekci et al.[95] and Bodenheimer et al.[112] In the latter's study, in which the effects of coronary reperfusion were examined, not only did (1) epicarcial TQ-ST segments normalize when the ligated artery was perfused distally with blood or normal saline and (2) reappear when reperfusion was stopped, but also (3) reperfusion after 1 or 3 hours of coronary occlusion failed to reverse and actually accelerated the development of new Q waves and the deterioration of tension in the ischemic zone.[112]

Ventricular arrhythmias and conduction disturbances: Ectopic pacemaker activity and conduction disturbances are most frequently associated with episodes of acute myocardial ischemia and infarction. Reliable diagnosis of infarction in such instances may be difficult, and attempts to quantify the TQ-ST segment deflection are best avoided. Intraventricular conduction block, for example, is often observed during major coronary occlusions[4] or with episodes of Prinzmetal's variant angina pectoris.[95] Changes in the temporal[203] or spatial[76] pathways of ventricular depolarization through the ischemic area may account for the block, the S wave and the S-T segment elevation usually observed during ischemia often being obliterated.[4] The presence of conduction delay has forced some investigators to eliminate electrograms exhibiting this phenomenon from their data on TQ-ST deflections.[4,125]

Preexisting TQ-ST segment deflections: These electrocardiographic abnormalities, unlike those previously considered, often exhibit many of the features generally attributed to ischemia. Consequently, reliable electrocardiographic characterization of the ischemic process is difficult. In clinical situations the history (digitalis intake), physical examination (pericardial friction rub) and laboratory data (serum enzymes, X-ray film), and certain subtleties of the electrocardiogram (pacemaker spike), must be relied upon to help furnish the correct diagnosis.

In experimental situations in which epicardial electrograms are recorded, electrode artifact is an important consideration. In studies in which wires are either inserted[54] or manually held[58] against the epicardial surface when recording the electrogram, TQ-ST deflections may arise from local mechanical trauma or pressure exerted by the electrode on the heart's surface and may not be simply distinguished from those arising from the coronary occlusion.[204] As expected from solid angle

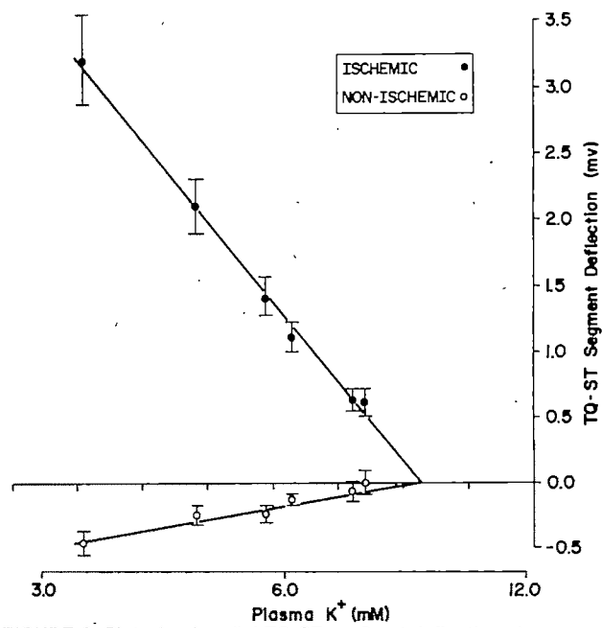


FIGURE 9. Plot of epicardial TQ-ST segment deflection changes recorded during multiple occlusions of the left anterior descending artery in the pig at steadily increasing plasma potassium (K^+) levels. The TQ-ST segment magnitude recorded from both ischemic (cyanotic) and nonischemic areas appears to vary with the log of the K^+ level. Values are expressed as mean ± standard error of the mean. Ten electrodes overlay the ischemic and seven the nonischemic areas.

considerations, a very small area of epicardial injury can result in TQ-ST deflections of considerable magnitude.[69] The importance of electrode selection and application in such studies should not be discounted.

Correlation Studies and TQ-ST Segment Mapping

Correlation—A mathematical statement of the kind and degree of relation between two or more variables.[205]

Correlation of TQ-ST deflection and other markers of ischemic injury: It is generally appreciated that after acute coronary artery occlusion the sites of TQ-ST segment elevation are *usually* observed to overlie tissue in the distribution of the occluded artery.[72,94,206,207] That this tissue has become ischemic can be demonstrated by its production of lactate,[56] ATP, creatine phosphate (CP) and CK depletion,[50,56,206] histologic abnormalities,[206,208] QRS complex alterations[76,95,203] and reduced oxygen tension,[72,128] contractile activity[209] and myocardial blood flow.[49,207,210–213] What may not always be appreciated are indications that (1) the absence of TQ-ST segment elevations does not rule out the presence of underlying ischemic injury,[83,207,208,210] and (2) *quantitative* correlations existing between the magnitude of the elevation at a particular site and the alternate markers of ischemic injury listed above are seldom seen. For example, although Hirschfeld et al.[214] and Maroko et al.[50] reported in early studies that epicardial TQ-ST segment elevation recorded 15 minutes after occlusion was inversely related to tissue CK depletion at 24 hours, other studies do not demonstrate this.[125,206] Data from Ginks et al.[206] showed that CK depletion was similar whether obtained from biopsy sites having TQ-ST elevations in the range of 2 to 4 mv or from those registering elevations in excess of 10 mv. In the same study, it was established that sites of elevation were associated with the later development of histologic abnormalities indicative of necrosis, but the *degree* of the abnormality could not be correlated with the *magnitude* of the elevation.

In a study on various biochemical markers of ischemic injury, including lactate accumulation and ATP and CP depletion, Karlsson et al.[56] concluded that "no direct relationship existed between the degree of lactate accumulation at a biopsied site and the magnitude of the S-T segment elevation at the same site." The same conclusion was drawn regarding ATP and CP depletion.[56]

Studies comparing the magnitude of the TQ-ST segment elevation to myocardial blood flow are more difficult to evaluate because of the variety of techniques used to measure the flow and the time after the occlusion when the measurements are made.[6] Although Kjekshus et al.[49] found a linear relation between the height of TQ-ST segment elevation recorded 15 minutes after coronary occlusion and reductions in subepicardial blood flow measured 24 hours later, this finding was not supported by the more recent work of Heng et al.[212] Correlations were also absent when measurements of blood flow were made at 15 minutes[207] and 120 minutes[211] after coronary occlusion, although sites of reduced flow did correlate well with CK depletion at 24 hours.[212]

TQ-ST deflection and contractile activity: Simultaneous measurements of electrograms and contractile activity in the ischemic region repeatedly indicate that mechanical changes are dissociated in time from TQ-ST segment changes in relation to onset of ischemia, degree of the abnormality during occlusion and the return of activity with subsequent reperfusion after various periods of ischemia.[36] Although contractile activity decreases almost linearly with reductions in coronary blood flow,[215,216] TQ-ST segment deflections seldom appear until after flow is reduced by 50 percent.[210,216] With release of a brief occlusion the TQ-ST segment deflections may[216] or may not[209] return toward normal within a few beats; however, return of normal contractile activity is often delayed[216] and there may be a prolonged or permanent deficit if the occlusion is maintained for as little as 10 minutes.[217–219] Finally, some recent discussion[36] indicates that pharmacologic interventions that improve contractile performance in

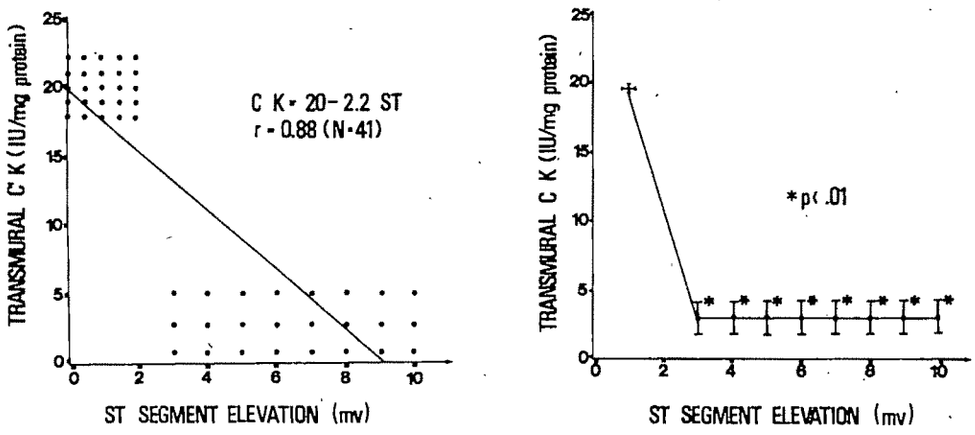


FIGURE 10. Hypothetical example of the relation between S-T segment elevation 15 minutes after occlusion and CK activity at the same site 1 week later. At nonischemic sites the elevation was 2 mv or less and at ischemic sites it was 3 or more mv. A linear regression analysis was performed **(left).** The *r* value computed (0.88) suggests that CK activity and S-T segment elevation are inversely related. A *t* test of the data was also performed **(right).** Although sites of S-T segment elevation were associated with later CK depletion, the *magnitude* of that elevation was not predictive of the degree of CK depletion. N = number of biopsies.

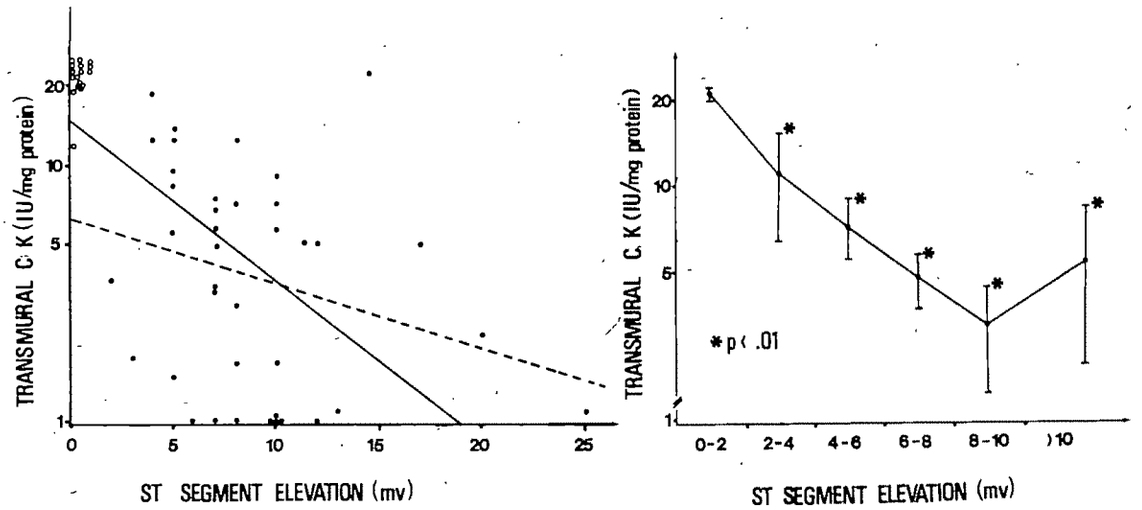


FIGURE 11. Relation between S-T segment elevation 15 minutes after occlusion and CK activity at the same site 1 week later. Data redrawn from Ginks et al.[206] A linear regression analysis of the data is shown at the **left.** The solid regression line (log CK = −0.06127 ST +1.17; $r = 0.66$; 56 biopsies) was computed by Ginks et al.[206] using both "ischemic" (**closed circles;** more than 2 mv) and "nonischemic" (**open circles;** 2 mv or less) sites. We have computed an additional regression line (log CK = −0.025 ST +0.78; $r = 0.27$; 38 biopsies) using only the "ischemic" sites **(broken line).** The t value of 1.68 for the latter correlation coefficient ($r = 0.27$) was not significant ($P = 0.09$). A t test of the data is shown at the **right.** Although sites of S-T segment elevation were associated with later CK depletion, the *magnitude* of that elevation was not predictive of the degree of CK depletion.

the ischemic region may actually worsen the electrocardiographic indications of injury.

Clinical correlations: Correlations with the TQ-ST segment deflection have been studied in clinical situations. Nielsen[2] reported that rates of cardiac arrest, cardiogenic shock and death were higher in patients with "major" TQ-ST segment elevations than in those with "minor" ones in the standard leads. However, other precordial mapping studies[8,53] do not support these specific findings although Madias et al.[53] did indicate that a relatively good correlation existed between summed TQ-ST segment deflections and clinical class (Killip criteria) in eight patients. Madias et al.[53] also reported the absence of any correlations between TQ-ST segment deflection magnitudes and serum creatine kinase, serum glutamic oxaloacetic transaminase and lactic dehydrogenase values after anterior transmural myocardial infarction.[8,53]

Limitations of statistical analysis of correlative data: Inappropriate analysis of data with use of regression procedures may lead to spurious and misleading conclusions regarding the closeness of linear relation between the TQ-ST segment deflection and alternate markers of ischemia. As an example, in Figure 10 (left) we have plotted data from a *hypothetical* study in which the tissue CK levels determined 1 week after coronary occlusion are plotted against the epicardial TQ-ST segment magnitude at the biopsy sites 15 minutes after occlusion. In the normal nonischemic region we have assumed that the TQ-ST elevation does not exceed 2 mv and that CK levels of 18 to 22 international units (IU)/mg protein are measured. In the ischemic/infarcted regions tissue CK levels show depletion with levels of 1 to 5 IU/mg protein; however, the TQ-ST elevation exhibits a wide spectrum of values ranging from 3 to 10 mv. A surprisingly high correlation coefficient ($r = 0.88$) was computed and an inversely linear relation between tissue CK levels and the TQ-ST segment elevation is suggested. However, if the data are replotted and a t test is performed (Fig. 10, right), it becomes clear that although sites of TQ-ST segment elevation (3 mv or more) overlie regions of later CK depletion, the *magnitude* of that elevation is in no way predictive of the degree of CK depletion.

According to Snedecor and Cochran,[220] in order for the correlation coefficient to be meaningful, one must first be assured that the regression is linear, which in this instance it is not. Furthermore, in order for the regression to be legitimately carried out in the first place, the variables must have been sampled from a single homogeneous population. The assumption that the ischemic and nonischemic regions together represent such a sample is highly unlikely. In practice, the nonischemic region S-T segment elevations rarely exceed 2 mv[50,83,206] and CK levels (or histologic findings, lactate determinations) show far less variation than they do in the ischemic region. If regressions are carried out for the ischemic and nonischemic sites separately in this example, the computed r values and slopes drop to zero. This would not have occurred if a linear relation truly existed and the ischemic and nonischemic samples were representative of a single bivariate homogeneous population of S-T segment and CK values.

Analysis of actual data yields similar findings. Figure 11 shows CK and S-T segment data replotted from Ginks et al.[206] Although the reported correlation coefficient ($r = 0.66$) suggests that an inverse linear relation exists between these two variables, a t test of the same data does not (Fig. 11, right). The data points shown were assembled not only from both ischemic and nonischemic regions, but also from several dogs. The requirement that these variables be sampled from a single homogeneous population again may not have been satisfied. If the regression line is computed for the "ischemic sites" (S-T greater than 2 mv) alone (Fig. 11, left; dashed line) and com-

TABLE V

Chi Square Test of S-T Elevation at 15 Minutes and Creatine Kinase (CK) Levels at 1 Week after Acute Coronary Artery Occlusion*

Comparison of CK Levels at Ischemic and Nonischemic Sites		
	CK (>18 IU)	CK (<18 IU)
Nonischemic sites (S-T ≤ 2 mv)	16	2
Ischemic sites (S-T > 2 mv)	2	36
Chi square = 39.2; no. = 56; *df* = 1; *P* <0.001		
Comparison at Ischemic Sites With Minor and Major S-T Segment Elevation		
	CK (>5 IU)	CK (≤ 5 IU)
Minor elevation (S-T ≤ 6 mv)	7	3
Major elevation (S-T > 6 mv)	13	15
Chi square = 0.83; no. = 38; *df* = 1; difference = not significant		

*Data from Ginks et al.[206] Chi square test with Yate's correction.[221]

pared with the original line computed for all sites, it is found that both the slope and intercept have changed significantly ($P < 0.01$) and the correlation coefficient has an insignificant value ($P = 0.09$). This suggests that (1) the original sample was not drawn from a single homogeneous population, and (2) the relation between the two variables is not linear.* In doing this we have effectively asked whether or not the *magnitude* of the S-T segment elevation in the ischemic region is useful in predicting the *degree* of later CK depletion. Although the *t* test indicates that sites of elevation usually overlie sites of CK depletion, the two variables do not appear, on the basis of these data, to be related to one another in a *quantitative* fashion.

The possibility that a *qualitative* relation might exist was by no means excluded and was subsequently investigated with use of the chi-square test shown in Table V. Although a comparison of CK levels at nonischemic and ischemic sites indicated that at the latter sites there was a strong likelihood of later CK depletion ($P < 0.001$), a second comparison of CK depletion at ischemic sites failed to demonstrate that sites of "major" (S-T more than 6 mv) elevation experienced greater depletion than those sites of "minor" (S-T 6 mv or less) elevation.

Implications: Viewing the question of correlation and quantitative relations from a theoretical perspective, we recall that the magnitude of the TQ-ST segment deflection is determined by (1) the difference in transmembrane potential existing at the *boundary* between the normal and ischemic regions, and (2) the relation of the recording electrode to that *boundary*. It is unreasonable, then, to expect the TQ-ST deflection to reflect other ischemic changes occurring in segments of tissue immediately adjacent to or underlying the electrode. Although the magnitude of the TQ-ST deflection varies depending upon its orientation with respect to the boundary, there is no reason to expect CK levels, histologic findings, lactate levels, tissue blood flow or other factors to vary in the same manner. The only factors associated with ischemia that might be expected to correlate with the TQ-ST deflection are those that have been implicated in the establishment of the transmembrane potential difference at the boundary. These, of course, would include the extracellular K^+ [83,163] and oxygen tension[128] gradient existing between the two regions for which relations have been noted.

* It should be recognized that similar inappropriate analysis may have been carried out in the course of some studies in which a *lack* of correlation of the TQ-ST segment deflection with alternate markers of ischemic injury had been observed.[207,212]

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Addenda

A. Downar et al.[222] have observed that an unknown substance present in the venous effluent from the ischemic segment in the pig is capable of depressing normal myocardial cells in much the same manner as if they were exposed to an extracellular potassium concentration of 16 millimolar.

B. In the recent investigation of Rau et al.[223] dealing with the mechanism of anoxia-induced potassium losses from ventricular muscle it was shown that (1) potassium loss began within seconds of the onset of anoxia, (2) the function of the membrane Na^+-K^+ pump is maintained through 60 minutes of anoxia, and (3) the entire net potassium loss out of the anoxic tissue was attributable to increased efflux from the cells.

C. It has been demonstrated recently that increases in intracellular calcium concentration in cardiac cells due either to ionophoretic injection of calcium (Ca^{++}) or Na^+ ions,[224,225] metabolic poisoning[226] or the administration of high concentrations of ouabain (2×10^{-6} molar)[227] result in a loss of electrotonic coupling between adjacent cells. This loss of coupling is believed to reflect a decrease in gap junction conductivity because of structural alterations in the geometry and spacing of apposed junctional membranes.[228,229] From the viewpoint of the solid angle theorem, a decrease in gap junction conductivity will, in turn, decrease the conductance term K in the equation shown in Figure 4. The decrease in the magnitude of the TQ-ST segment deflection recorded in the hours to days after acute myocardial infarction may in part be accounted for on this basis.

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Mitral Valve Aneurysm After Infective Endocarditis in the Billowing Mitral Leaflet Syndrome

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Mitral valve aneurysm is an uncommon complication of infective endocarditis. This report describes a patient with severe regurgitation due to perforations in a mitral aneurysm who required mitral valve replacement 9 years after a staphylococcal infection was superimposed on a billowing mitral leaflet. The unusual auscultatory signs and angiographic appearance could have led to diagnosis of the aneurysm.

Aneurysm of the mitral valve has been recognized for at least 130 years[1] but is an uncommon cause of mitral regurgitation. Many reported cases[1–5] occurred in association with aortic valve disease, and the aneurysm was believed to be caused by extension of infective endocarditis of the aortic valve onto the anterior leaflet of the mitral valve. Most instances of mitral valve aneurysm with a normal aortic valve are also a sequel of infective endocarditis although evidence of past inflammation has not been detected in all cases.[6,7] Since the relatively recent observation that the billowing mitral leaflet syndrome is commonly found in cardiologic practice,[8–10] there have been several reports of infective endocarditis occurring with this mild hemodynamic abnormality.[11–13]

This paper describes further details of a case of billowing mitral leaflet syndrome, previously briefly reported from this laboratory,[13] in which infective endocarditis resulted in severe mitral regurgitation associated with a large perforated aneurysm of the anterior mitral valve leaflet. Some auscultatory and other features of the valve aneurysm are discussed.

Case Report

A white woman, pregnant 24 weeks, was first seen in this clinic in 1959 at age 27 with a complaint of palpitations. Apart from an isolated nonejection systolic click, confirmed phonocardiographically, the physical examination was normal. An electrocardiogram showed a mean frontal plane QRS axis of +30° with T wave flattening in lead II and T wave inversion in leads III and aVF. The patient was reassured about her cardiac status and temporarily lost to follow-up study. In September 1965 she underwent a dilatation and curettage after a spontaneous abortion. In May 1966 she returned to this clinic noting that several episodes of central chest pain, each lasting about 1 minute, had occurred during the previous 3 weeks. The pain was associated with sweating, rapid palpitations and shortness of breath. She had also noticed increasing tiredness, breathlessness on effort and intermittent joint pains. She volunteered that the tips of her fingers had become swollen, hot and painful.

On admission, she did not look ill but had marked clubbing of her fingers and was pyrexial. There was no evidence of heart failure. The pulse was 96/min, regular and of normal volume. The blood pressure was 110/80 mm Hg. The apex beat was in the fifth interspace within the midclavicular line, and no abnormal precordial pulsations were detected. The mitral component of the first heart sound was soft, and a grade 2/6 pansystolic murmur that was accentuated in late systole, a soft third heart sound and a short mid-diastolic murmur were heard

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at the apex. The second heart sound was normal. The spleen was palpable. The ankle and knee joints were slightly tender but not swollen. On subsequent examinations, during the patient's hospital stay of 2 months, the apical systolic murmur was often confined to late systole and a nonejection systolic click was heard.

The electrocardiogram was similar to that recorded 7 years previously except for evidence of first degree heart block with a P-R interval of 0.29 to 0.38 second. A chest roentgenogram was normal; the cardiothoracic ratio was 43 percent. The blood count was normal. The erythrocyte sedimentation rate (Westergren) was 40 mm in 1 hour, C-reactive protein 2+ and mucoprotein 290 mg/100 ml (normal 45 to 125 mg/100 ml). The antistreptolysin titer was 50 units/ml. A diagnosis of infective endocarditis was made, and three successive blood cultures grew staphyloccus albus. Therapy with parenterally administered penicillin and streptomycin resulted in dramatic improvement; the temperature returned to normal and the clubbing regressed. The P-R interval had shortened to 0.21 second at the time of discharge from hospital. One month later, examination revealed that the systolic murmur had increased in intensity to grade 4/6 and was pansystolic with maximal accentuation in mid-systole.

The phonocardiogram (Fig. 1) confirmed the crescendo-decrescendo configuration and showed two major left-sided components of the first heart sound, occurring 0.05 and 0.07 second, respectively, after the Q wave of the simultaneous electrocardiogram. The second heart sound was split (0.05 to 0.06 second) with accentuation of the pulmonary component. In addition there was now a loud left ventricular third heart sound and a presystolic murmur.

Cardiac catheterization in January 1969 confirmed the presence of severe mitral regurgitation with no diastolic pressure difference across the mitral valve (simultaneous left atrial and left ventricular pressures). Left ventriculograms, in both right and left anterior oblique views, were interpreted as showing marked prolapse of the mitral valve secondary to ruptured chordae tendineae. In retrospect the area thought to show maximal prolapse clearly indicated an aneurysm of the anterior leaflet; in addition there is marked scalloping of the posterior mitral leaflet.

During the next 6 years the patient gradually became more symptomatic but was reluctant to undergo surgery. A prominent presystolic murmur remained. Serial chest roentgenograms demonstrated a progressive increase in the cardiothoracic ratio to 60 percent with evidence of left ventricular, left atrial and right ventricular enlargement and pulmonary venous hypertension. In March 1975 the patient was admitted to the hospital with pulmonary edema and then consented to surgery.

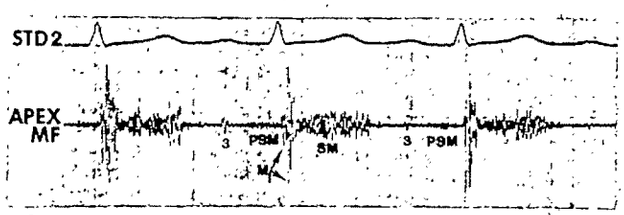


FIGURE 1. Medium frequency (MF) phonocardiogram recorded at the cardiac apex in October 1966. Two major left-sided components (M_1 **arrowed**) of the first heart sound, a third heart sound (3) and presystolic (PSM) and crescendo-decrescendo systolic (SM) murmurs are shown. Time lines are 0.04 second apart. STD 2 = standard lead II of the electrocardiogram.

At operation, the aortic valve was normal. The posterior leaflet of the mitral valve (Fig. 2) was voluminous and markedly scalloped. The anterior leaflet was also voluminous and the medial half of this leaflet was aneurysmal (Fig. 2). The aneurysm, 2 cm in diameter, had two perforations 1.0 and 0.5 cm in diameter, respectively, at the apex. Some of the chordae tendineae were elongated but none had ruptured. The mitral valve was excised and replaced with a Bjork-Shiley prosthesis. Postoperatively the patient has remained well. Microscopic examination of sections taken from both leaflets showed foci of degeneration that stained positively with Alcian blue, indicating an increase in acid mucopolysaccharide content. Only a minimal increase in fibrous tissue was seen and there were no Aschoff nodes. Sections of the papillary muscles showed hypertrophy of individual muscle fibers with numerous areas of interstitial fibrosis.

Discussion

The occurrence of bacterial endocarditis on minimally abnormal valves,[14] particularly in the elderly,[15] is well recognized. Recently, infective endocarditis has been reported[12,13] in patients with the billowing mitral leaflet syndrome, some of whom had an isolated nonejection click as the only detectable clinical abnormality.[11,13]

Our patient initially presented with features of the billowing mitral leaflet syndrome, namely, palpitations and an isolated nonejection click with abnormal T waves in the inferior electrocardiographic leads. Seven years later she had bacterial endocarditis and we incorrectly attributed her progressive mitral regurgitation to rupture of chordae tendineae. We have observed[10] two major left-sided components of the first heart sound in patients with ruptured chordae tendineae and believe they result from asynchronous maximal tension on the

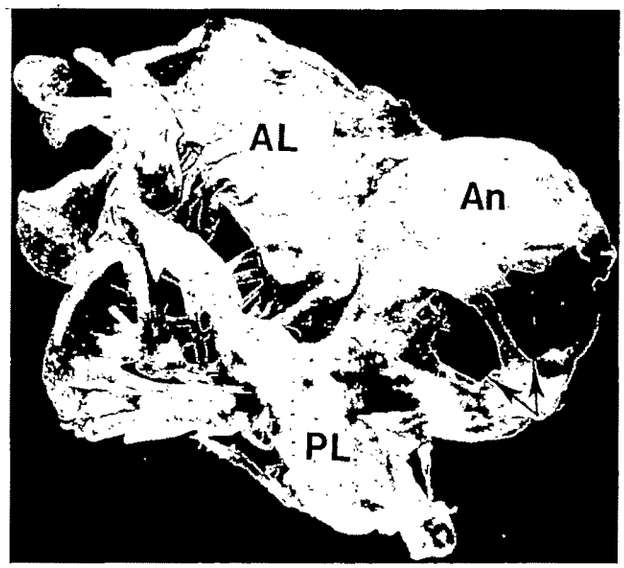


FIGURE 2. Excised mitral valve showing the voluminous anterior (AL) and posterior (PL) leaflets and the two perforations (**arrowed**) in the large aneurysm (An) involving the medial half of the anterior leaflet. Some of the chordae tendineae are thickened and elongated.

two mitral leaflets and their chordae. The two major left-sided components in our patient can probably be explained by asynchronous tensing of the relatively normal and aneurysmal portions of the mitral valve. However, the presence of a prominent presystolic murmur is most unusual in patients with pure severe mitral regurgitation caused by ruptured chordae tendineae; such patients typically have a third heart sound, often loud, that may be followed by an extremely short mid-diastolic murmur.[16] The presystolic murmur should have alerted us to the possibility of an aneurysm because we have previously encountered both a reduplicated mitral component of the first heart sound and a pressure difference across the mitral valve in an analogous situation in which a large pericardial patch had been inserted into the posterior leaflet.[10] Inversion of the patch into the left ventricle during diastole partially obstructed left ventricular inflow and was associated with loud mid-diastolic and presystolic murmurs. We did not record a diastolic or presystolic pressure difference in our patient but postulate that turbulence causing the presystolic murmur arose, at that time, from the inverted aneurysm. A similar mechanism would explain the diastolic murmur reported by Musallam and McCall[6] in a patient with a large aneurysm of the posterior leaflet of the mitral valve found at necropsy.

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Coexisting Right and Left Hypertrophic Subvalvular Stenosis and Fixed Left Ventricular Outflow Obstruction Due to Aortic Valve Stenosis

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A case of fixed left ventricular outflow tract obstruction due to aortic valve stenosis coexisting with right- and left-sided subvalvular hypertrophic stenosis is documented with hemodynamic data, angiograms, echocardiograms and findings at surgery. Histologic examination of the septal muscle with light and electron microscopy revealed hypertrophy of the muscle but none of the characteristics of idiopathic hypertrophic subaortic stenosis. Septal hypertrophy with subvalvular obstruction can occur secondary to left ventricular pressure overload due to fixed left ventricular outflow tract obstruction and is not always the chance occurrence of two separate diseases.

Cases of well documented fixed aortic valve obstruction in association with a subvalvular gradient are unusual. Because of the characteristic cell architecture of idiopathic hypertrophic subaortic stenosis, it has been postulated that these cases represent the coincidental coexistence of two separate disease entities. The following report presents a patient who had valve obstruction without the characteristic cell changes of idiopathic hypertrophic subaortic stenosis.

Case History

The patient, a 70 year old woman, had a 20 year history of a heart murmur with a recent history of fatigue and dyspnea on exertion. She had been having melena for 1 month and was admitted to another hospital for evaluation. Her hematocrit was 20 percent. She was given blood replacement. Contrast studies revealed diverticulosis of the colon. Because of a grade 4/6 systolic ejection murmur and cardiomegaly, she was transferred to this center for further evaluation. Prior medications were propranolol, 20 mg twice daily, and digitoxin, 0.2 mg daily. On the day of transfer, the patient was lethargic and her medical history was difficult to obtain. She complained of fatigue, two pillow orthopnea and frequent palpitations accompanied by chest discomfort. There was no family history of cardiovascular disease.

Physical examination revealed a blood pressure of 90/60 mm Hg with decreased central pulse amplitude and pulse pressure but no delay in pulses. The jugular venous pressure was not increased. The point of maximal impulse was deviated to the left of the mid clavicular line and thrusting; a fourth sound gallop could be palpated. A grade 4/6 harsh systolic murmur at the cardiac apex radiated to the left sternal border and to both carotid vessels. No diastolic murmurs were heard.

Laboratory data revealed a normal hematocrit and a blood urea nitrogen of 25 mg/100 ml. The chest roentgenogram showed cardiomegaly with left ventricular prominence, prominence of the ascending aorta and clear lung fields. The electrocardiogram revealed first degree atrioventricular (A-V) block and left ventricular hypertrophy with strain. The echocardiogram disclosed left ventricular hypertrophy, a calcified aortic valve, a decreased E to F slope (46 mm/sec), systolic anterior motion of the anterior leaflet of the mitral valve, and a septal to posterior wall thickness ratio of 1.4 to 1 (Fig. 1).

Cardiac catheterization: The patient continued to do poorly, and cardiac catheterization was performed. There was a pressure gradient of 120 mm Hg across the aortic valve, and an additional subvalvular gradient of 90 mm Hg. In the right ventricle there was a 15 mm Hg subpulmonary gradient. The cardiac output was reduced as calculated by both the Fick and the green dye methods.

Cardiac fluoroscopy revealed heavy calcification of the aortic valve. A left ventriculogram in the right anterior oblique projection revealed almost complete

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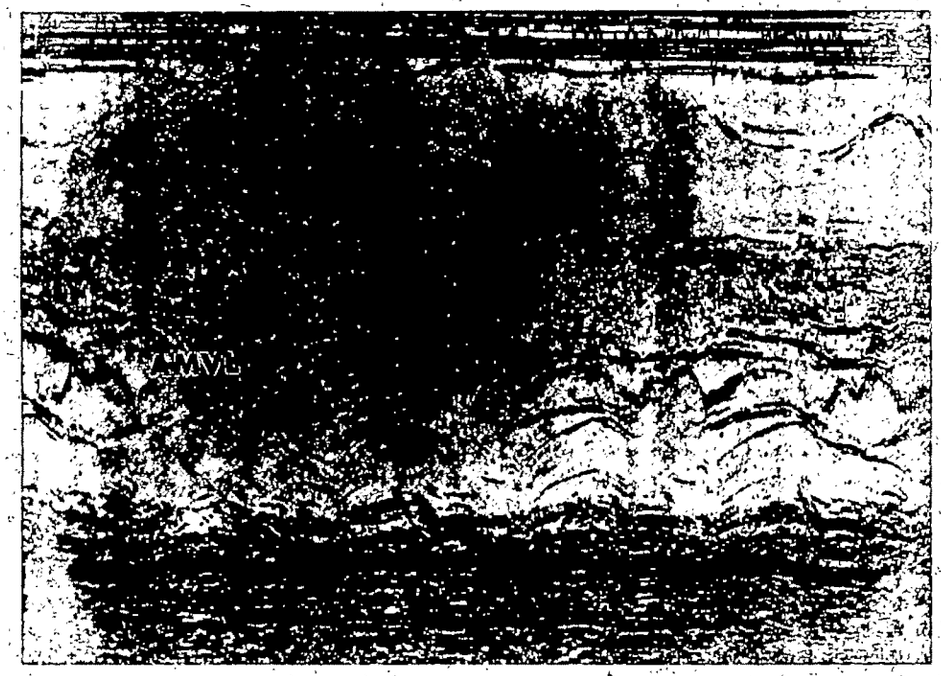


FIGURE 1. Preoperative echocardiogram disclosing asymmetric septal hypertrophy, and systolic anterior motion and diminished E to F slope of the anterior mitral valve leaflet. AMVL = anterior metral valve leaflet; IVS = interventricular septum.

obliteration of the left ventricular cavity during systole and an ejection fraction of 87 percent. There was a puff of mitral insufficiency. Simultaneous right and left ventriculograms revealed an extremely large septum with systolic narrowing of both the left and right outflow tracts. Aortic root injection revealed a puff of aortic insufficiency, a distorted aortic valve with a small anulus and poststenotic dilatation of the aortic root. Coronary angiograms were normal.

Surgical and histologic findings: Because of these findings and the clinical history, the patient underwent aortic valve replacement with a no. 21 porcine heterograft[1] as well as excision of subaortic hypertrophied muscle. Observations at surgery were marked hypertrophy of the left ventricle, an ascending aorta two times normal size, an aortic valve with an opening 3 to 4 mm in diameter and subaortic outflow tract obstruction. Segments in the muscle were cut from the septum

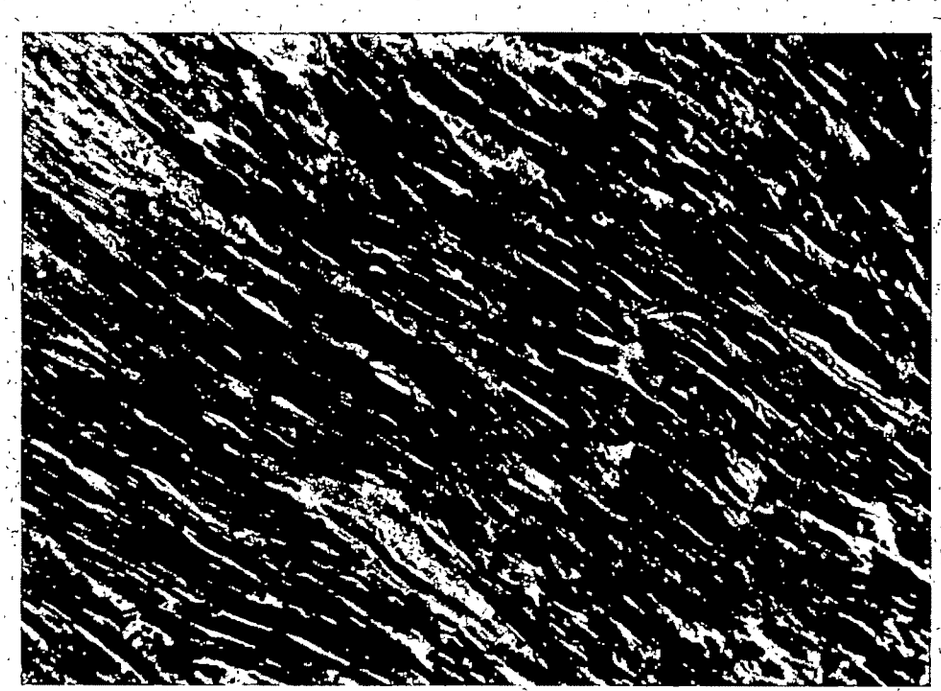


FIGURE 2. Light photomicrograph of septal muscle tissue showing hypertrophied muscle fibers in an orderly arrangement without evidence of the disarray seen in idiopathic hypertrophic subaortic stenosis. (Hematoxylin-eosin ×40, reduced by 24 percent.)

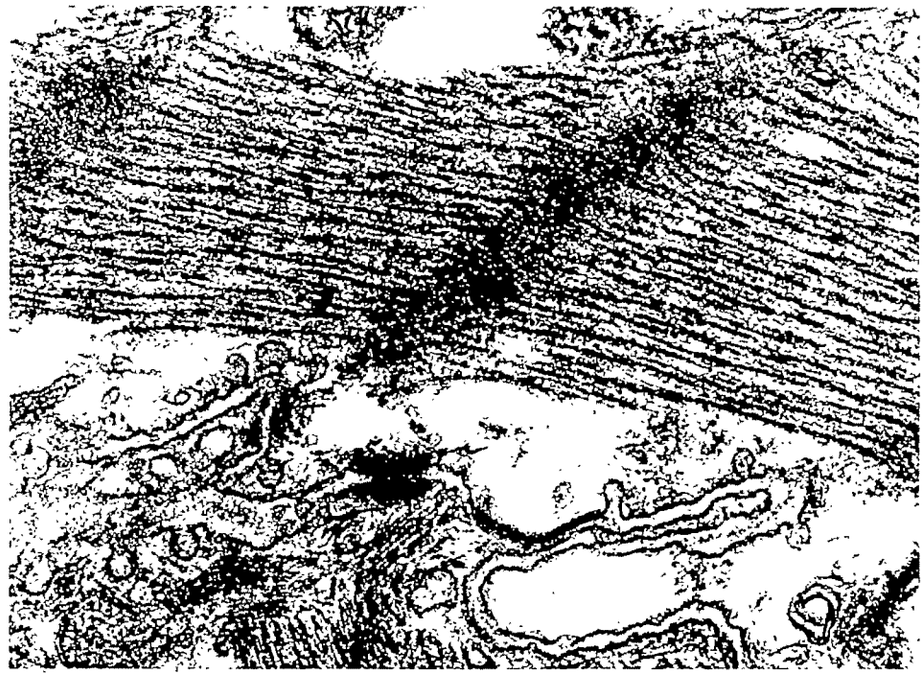


FIGURE 3. Electron photomicrograph of septal muscle tissue showing muscle fibers arranged in parallel without evidence of whorls or abnormal myocytic size or shape. (Osmium-uranil acetate lead citrate ×98,600, reduced by 23 percent.)

and left lateral wall in a circumferential area between the right and left coronary arteries. Myectomy was performed according to the technique of Morrow et al.[2] Two samples of muscle were preserved in formalin and glutaraldehyde for preparation for light and electron microscopy. Light microscopy disclosed mild myocardial hypertrophy and focal fibrosis (Fig. 2). Electron microscopy revealed that the fibers were arranged in parallel without evidence of whorls or disarray. The myofibrils showed minimal irregularity of the Z bands, and the myocytes appeared to have a normal number of mitochondria. Glycogen was present. The intercalated discs were intact (Fig. 3).

Discussion

The clinical presentation, hemodynamic findings and noninvasive observations of asymmetric septal hypertrophy and idiopathic hypertrophic subaortic stenosis have been well described.[3–6] Abnormalities of cell and myocardial architecture have been found in septal muscle and have been recognized as a microscopic indicator of this disease.[7–10] The muscle cells, which are in disarray, are found focally in the myocardium and are arranged in whorls or randomly. The cells themselves are irregular and of different sizes and shapes.

The coexistence of hypertrophic subaortic stenosis and fixed left ventricular outflow obstruction due to aortic valve stenosis is uncommon. Twenty-six cases have been reported,[11–19] many of them in children. In our patient the hemodynamically fixed and subvalvular obstructions were nicely demonstrated without provocative pharmacologic agents. The diagnosis was suspected before cardiac catheterization because of the asymmetric septal hypertrophy and systolic anterior motion of the anterior leaflet of the mitral valve in the echocardiogram. In most reported cases, the diagnosis was made operatively or suspected postoperatively when the patient's condition failed to improve after aortic valve replacement. Histologic examination of septal tissue was performed in only two of the reported cases. Both demonstrated many of the findings of idiopathic hypertrophic aortic stenosis with hypertrophy and disorderly array of the myocardial fibers, which branched and changed direction, forming loops and whorls.[19] These data provided supportive evidence for the coexistence of two distinct diseases.

Our patient had none of the histologic characteristics of idiopathic hypertrophic subaortic stenosis on either light or electron microscopy. This finding supports the hypothesis that in our patient the subvalvular obstruction on both the right and left sides was secondary to hypertrophy of the septum as a response to pressure overload due to aortic valve obstruction. Sufficient data are not available at this time to determine the frequency of occurrence of the two lesions independently and that of aortic stenosis with secondary subvalvular stenosis. The probability that the two lesions will occur simultaneously is the multiple of the probabilities of the independent occurrence of each disease, thus making the former an uncommon accident of nature. However, secondary hypertrophy with subvalvular obstruction commonly occurs in right-sided valvular lesions (pulmonary valve stenosis). That it could also occur on the left side is not unlikely because the same hemodynamics are involved.

Acknowledgment

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The Disputed S-T Segment Mapping: Is the Technique Ready for Wide Application in Practice?

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"I wish I could have attended to him sooner" or "I wish he had not waited that long." Such spoken or unspoken wishes are probably familiar to many cardiologists confronting refractory shock or congestive heart failure in the setting of recent myocardial infarction. At the root of such reflection is the impression that the clinical condition might have been less precarious if the treatment had commenced earlier. In all likelihood, these impressions stem from some personal clinical experience. This may be an observation that myocardial infarction tends to be more extensive and complicated after a difficult and protracted resuscitation than after a promptly terminated arrest or a recollection of some dramatic improvement in response to the relief of anxiety or pain, correction of an abnormally slow or rapid heart rate, suppression of an arrhythmia or skillful control of abnormal blood pressure. Because observations of this type are common in daily practice, clinicians are becoming receptive to the concept that the extent of myocardial infarction is not determined instantaneously at the onset of the episode but within a finite period of time during which some appropriate interventions can influence the final outcome of the pathologic process. The acceptance of this concept, pioneered by Eugene Braunwald, broadens the responsibility of the attending physicians whose action or inaction at the onset of acute myocardial infarction may critically affect not only the immediate, but also the long-term prognosis of their patients.

The titles of the editorials by Braunwald and his group—"Reduction of Infarct Size" [1] and "Protection of Ischemic Myocardium" [2]—have become household items in the vocabulary of most practicing cardiologists in this country. The origin of these concepts can be traced directly to the past two decades of progress in the understanding of cardiac function, myocardial energetics and coronary circulation. In many of these areas, the investigations of Braunwald and his collaborators have played a singularly important role in the formulation of new ideas. These ideas have introduced new diagnostic and therapeutic procedures that in turn have created new challenges for the practitioner. These challenges have become particularly evident in the changing philosophy of treatment of serious hemodynamic complications of acute myocardial infarction. In this setting, interventions, both old and new, tend to expose simultaneously both edges of the proverbial sword. For instance, an intervention designed to increase the perfusion pressure and flow within the ischemic area may cause an undesirable increase in myocardial oxygen consumption; conversely, an intervention designed to decrease myocardial oxygen consumption by decreasing afterload or myocardial tension may result in a deleterious decrease in perfusion pressure and flow. To the initial concern about the delicately balanced fate of the jeopardized myocardium has been added concern about the delicate balance between the salutary and harmful effects of specific interventions. No wonder that such therapy demands some means of rapid and precise scrutiny of the results. If the aim of treatment is protection of the injured myocardium, one must have some methods of measuring the extent of injury and some ways of monitoring the changes in the size of infarction. In the absence of such indicators, one cannot effectively evaluate the outcome of interventions. This brings me to S-T segment mapping.

S-T segment mapping has been introduced as potentially one of the most promising methods of rapidly estimating changing infarct size in clinical practice. The theoretical and practical aspects of this method are presented in depth by Holland and Brooks[3] in a comprehensive, scholarly and richly referenced review article in this issue of the Journal. They attribute the popularity of S-T segment mapping to its "low cost, noninvasive approach and simply applied rules of interpretation." One can argue perhaps that a procedure that is relatively simple to a clinical investigator, aided by engineers and computers, may appear complex to a nonacademic practitioner who has no consultants and no engineering support for establishing the S-T segment

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mapping procedure in the coronary care unit of his hospital. To map the S-T segment, Maroko et al.[4] used a blanket with 35 paste-filled cup electrodes connected to a special switchbox. Assuming that such a blanket and the switchbox are commercially available and that the setup does not require the services of an electrical engineer, the performer of mapping would like to have an estimate of the time required to record 35 consecutive leads and, more important, an estimate of the time needed to carry out the recommended measurements of the sum of S-T elevations in 35 leads. Can this be computed manually with ease or does it require a dedicated on-line computer? If it can be done manually, will the answers be available in time to make an impact on the patient's condition? Cardiologists must know the answers to these and perhaps certain other questions before applying the blanket with the 35 electrode cups or before marking the chest at 49 potential sites of electrode placement, as practiced in another institution.[5] Incidentally, someone should probably attempt to measure the added impact of such manipulations on the psyche of persons brought into the perplexing environment of our modern coronary care units.

Assuming that all of the above questions have been answered, and that the equipment necessary to perform the S-T segment mapping has been procured, one must ask the final and most important question: How reliable and informative is this procedure in estimating the changing size of the myocardial infarct? Answers to this question can be found in two adjoining editorials in the October 1976 issue of *Circulation.* Each of these editorials answers this question differently: In the first editorial, Braunwald and Maroko[6] state that ". . . until more accurate and convenient methods for assessing ischemic injury have been developed and validated," changes in the S-T segment "are likely to continue to provide *extremely helpful information* concerning the presence and extent of ischemic damage of the myocardium, both in experimental animals and in patients." In the second editorial, Fozzard and Das Gupta[3] conclude that inferences from the extent or magnitude of S-T changes overlying an area of ischemia may be misleading and that S-T segment mapping "*should not be used* as an independent measure of ischemia." The review of Holland and Brooks[3] assembles a considerable amount of background material that may explain the divergent opinions expressed in these two editorials. As reviewers, Holland and Brooks are not completely free of personal bias; their own electrophysiologic studies have convinced them that the theory of S-T segment mapping fails to provide a solid foundation for the application of this method in practice. However, their "bias" does not detract from the scientific accuracy of statements related to the theory and practice of S-T segment mapping. The review creates an impression that the aspects related to the practical value of S-T segment mapping may be more controversial than the theory underlying the procedure. Most of the theoretical aspects *do not,* or *should not,* cause much disagreement among investigators. The following list includes items of an expected consensus:

Accepted Factors That Determine Role of S-T Mapping in Clinical Practice

1. The electrophysiologic theory of S-T segment displacement in myocardial ischemia rests on a solid base of experimental data. The displacement of the S-T segment is caused by the "diastolic" and the "systolic" injury currents flowing between the ischemic and normal myocardium. The depolarization and the shortening of action potential, that is, the factors responsible for "injury currents," have been attributed to regional hyperkalemia produced by potassium leak from the injured cells. In agreement with this theory, my collaborators and I[8] found that very small doses of potassium salts infused into the coronary artery simulate the electrocardiographic pattern of acute ischemia by producing both S-T segment deviation and displacement of baseline in the electrograms recorded with direct current-coupled amplifiers. However, more recently the role of potassium has been challenged by the studies of Downar et al.,[9] who found, in the blood draining ischemic myocardium, a yet unidentified substance causing more serious electrophysiologic derangements than hyperkalemia. Identification of this substance will be undoubtedly of great importance but this discovery will not alter the principles of the electrophysiologic theory of S-T segment displacement.

2. The measurement of S-T segment displacement depends on the magnitude of "current of injury" and the orientation of the recording electrode with respect to the geometry of the ischemic boundary. The method of precordial mapping is designed primarily to monitor myocardial ischemia of the anterior wall and not of the inferior or posterior wall.

3. Myocardial ischemia is not the sole cause of S-T segment displacement. Therefore, evaluation of results may be difficult in the presence of other causes of displacement such as secondary S-T deviations due to intraventricular conduction disturbances or primary S-T deviations due to factors other than myocardial ischemia, for example, pericarditis, digitalis or hypokalemia.

4. Precordial S-T segment mapping cannot be considered a reliable method of sizing myocardial infarction. Even under the best circumstances, the S-T segment map can estimate only the surface area, not the mass, of the infarcted myocardium, and no consistent direct relation between these two measurements would be expected. Moreover, Holland and Brooks remind us that the estimate of the infarcted surface area depends critically on the location and proximity of the recording electrodes. Therefore, it is necessary to keep in mind that the predominant task assigned to S-T segment mapping is to indicate the changes in the extent of ischemia in a patient serving as his own control, and not to make comparisons among infarct sizes in different patients.

5. Sensitivity of S-T segment elevation to reduction of coronary blood flow is limited. Experimental studies[10] showed that even in direct epicardial leads, S-T segment elevation occurred only after local myocardial flow was

reduced below 50 percent of control level, and that intramural recordings were more sensitive than epicardial leads. It is obvious that precordial S-T segment mapping is not designed to monitor myocardial blood flow.

6. It is essential to remember that the S-T segment map in a patient with acute myocardial ischemia can be affected by many variables other than the area of ischemic zone. These include in particular (a) electrophysiologic changes in the myocardium outside of the ischemic area; (b) various combinations of cancellations of "currents of injury" in different portions of the ischemic myocardium; (c) electrophysiologic effects of ischemia other than "currents of injury," for example, local conduction disturbances and arrhythmias; (d) effect caused by the presence of necrotic nonexcitable myocardium; (e) specific effects of scars and aneurysms; (f) changes in ventricular wall thickness; and (g) various preexisting electrocardiographic abnormalities.

7. The evolution of S-T segment deviation after acute myocardial infarction varies in different persons. Recently, Mills et al.[11] reported that in about 60 percent of patients with anterior wall infarction the S-T segment elevation fails to regress within 2 weeks and that persistent S-T elevation is associated with more severe infarction. Thus, the persistence of S-T elevation may complicate the evaluation of S-T segment mapping in a sizable group of patients in whom the clinicians may be most interested in the "salvage" of the ischemic myocardium.

Areas of Controversy: Unanswered Questions

The total sum of the factors that limit the application and modify the results of S-T segment mapping will probably determine the ultimate role of this method in practice. However, these factors in themselves are not the subject of controversy. The divergence of opinions and the dispute about S-T segment mapping rest on the following two questions:

1. Does S-T segment mapping provide useful clinical information in spite of all known theoretical and practical limitations of the method? In other words, even if we cannot expect perfect correlations, can we still obtain useful indications of trends?

2. Is the usefulness of the method validated by animal studies that correlate the results of S-T segment mapping with other independent measurements of infarct size?

At this time, both questions are unanswered:

1. Clinical studies, reviewed by Holland and Brooks,[3] report both good and poor correlations between S-T segment changes and other indicators of myocardial infarct size. The results of published studies in which S-T segment mapping has been used to evaluate the effects of treatment have not yet demonstrated that S-T segment elevation is an independent indicator of prognosis or a marker of trends. Some articles show statistically significant results, but their implications are not immediately obvious. For instance, in the study of Madias et al.,[12] breathing pure oxygen for 60 minutes reduced the sum of S-T elevations but the maps returned to control value after oxygen inhalation was discontinued. Is one to conclude that oxygen inhalation decreased the size of the infarct and that the discontinuation of oxygen inhalation increased it again to previous size? In another study, Chiariello et al.[13] found that treatment with sodium nitroprusside decreased pulmonary capillary wedge pressure but increased the sum of S-T segment elevations. Is one to conclude that nitroprusside was beneficial in the relief of left ventricular failure but increased the infarct size?

2. It has been pointed out repeatedly that the model of myocardial infarction produced by coronary ligation in anesthesized animals does not necessarily simulate myocardial infarction in man with diffuse coronary artery disease. Therefore, correlations between the S-T segment maps and infarct size in dogs do not prove that similar correlations must be present in myocardial infarction in man. Moreover, recently Irwin and Cobb[14] reported that the precordial S-T segment changes 15 minutes and 2 hours after occlusion of the left anterior descending coronary artery in awake dogs are not sensitive or specific predictors of transmural and epicardial infarction. Other studies from the same laboratory[15] show a poor correlation between the anatomic infarct size and the estimate of myocardial enzymes and cast doubt on the validity of conclusions based on the correlations between the estimates of myocardial enzymes and S-T segment changes.[6]

Conclusions: Electrophysiologic theory explains adequately both the genesis of S-T segment displacement in acute myocardial infarction and the possible modifications of this displacement by various physical, physiologic, pathologic, pharmacologic and clinical variables. The large number of variables as such does not disqualify the method but does indicate that under certain circumstances the procedure may be useless or misleading. S-T segment mapping should not be prematurely dismissed because it may serve as a useful indicator of trends in a certain group of patients under certain well defined circumstances. Clinical studies are needed to define these groups of patients and these clinical circumstances. However, in the absence of such information, the mapping of S-T segments is not ready for wide clinical application.

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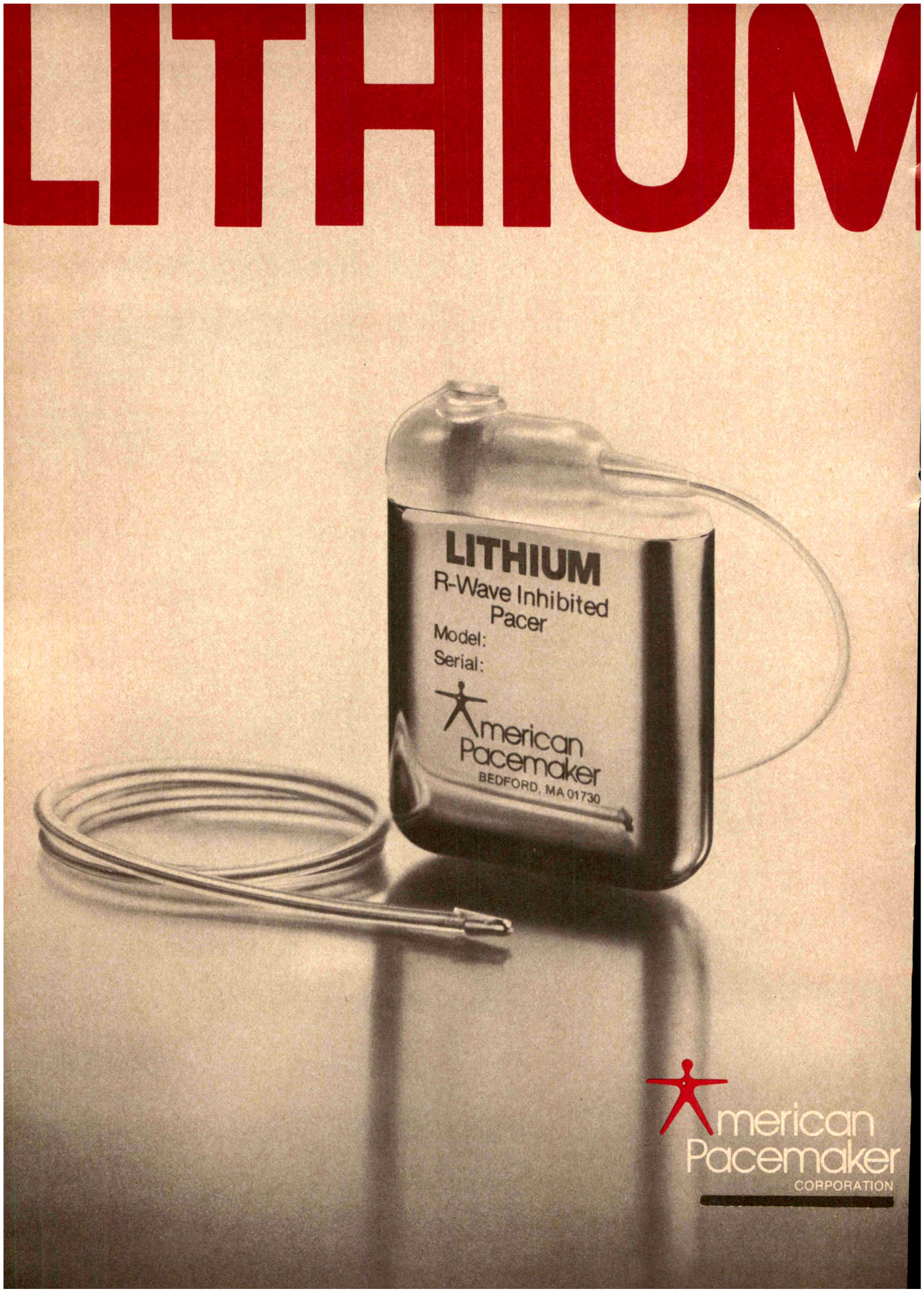
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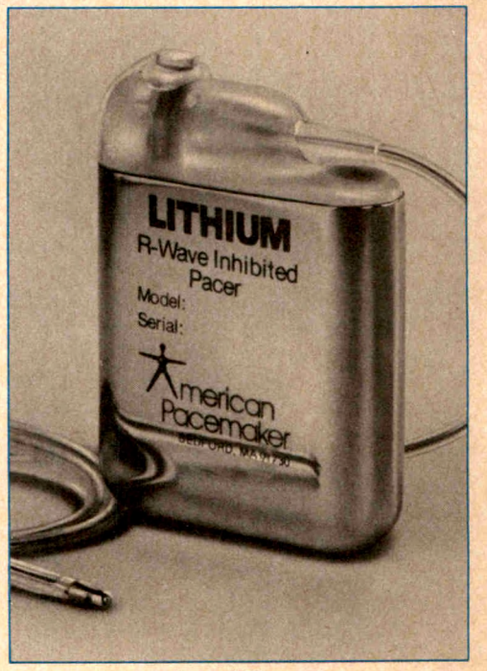
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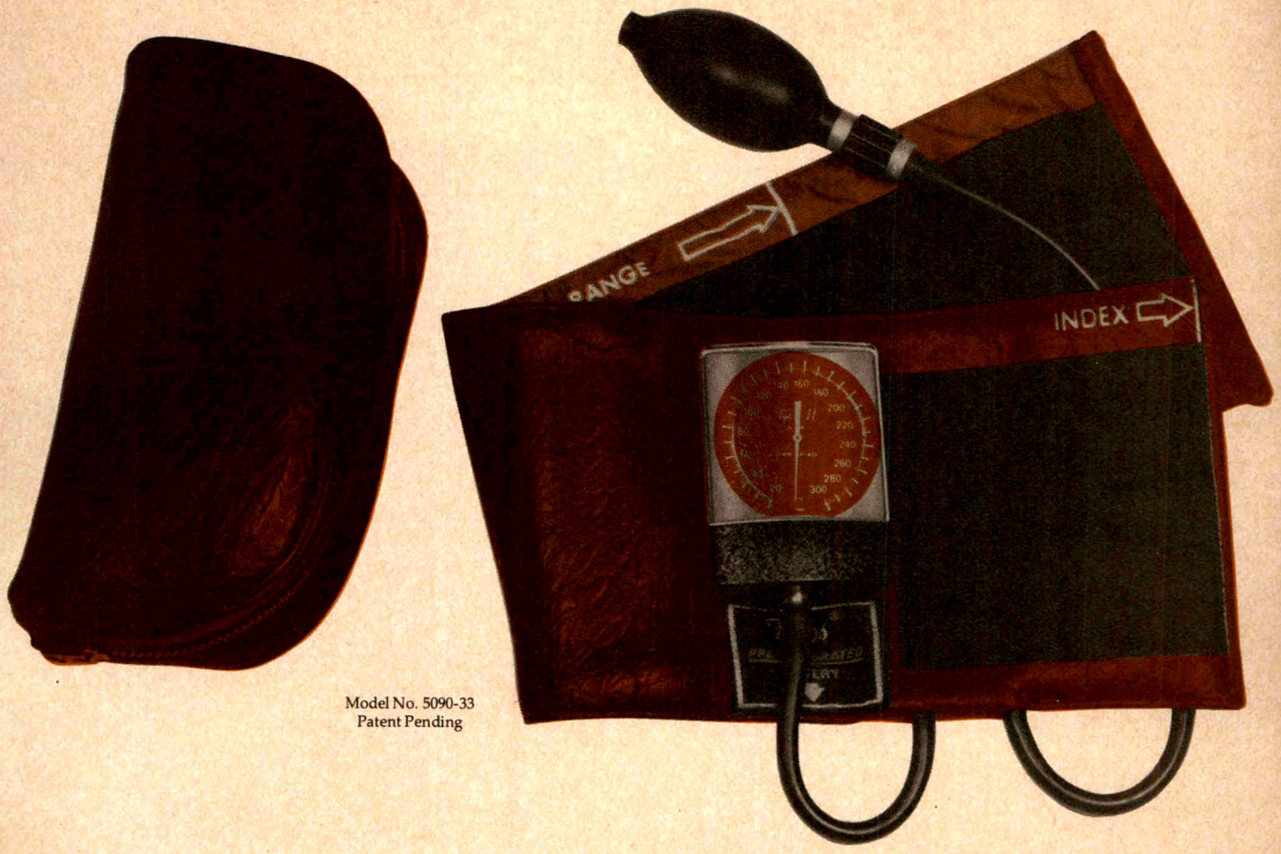
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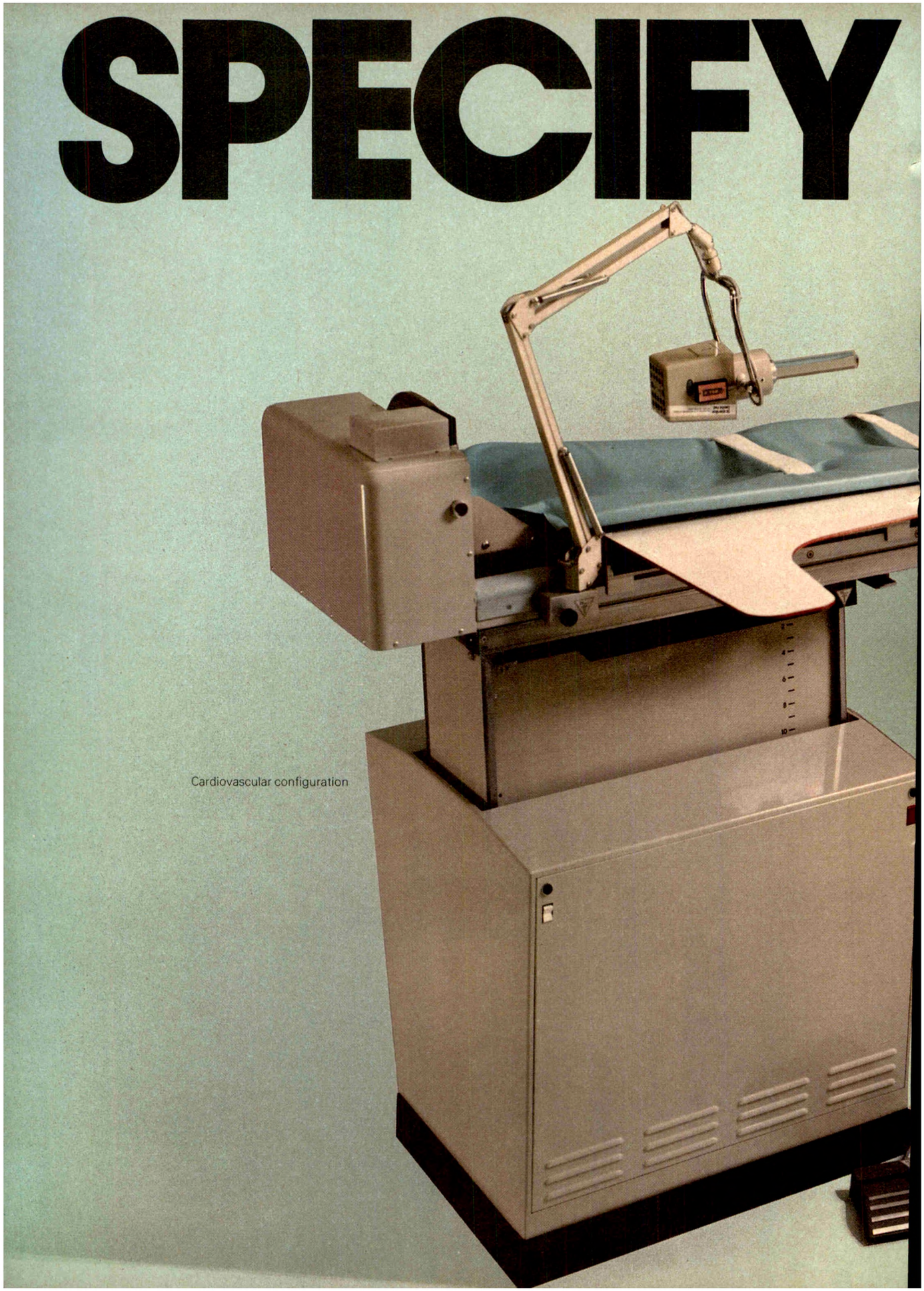


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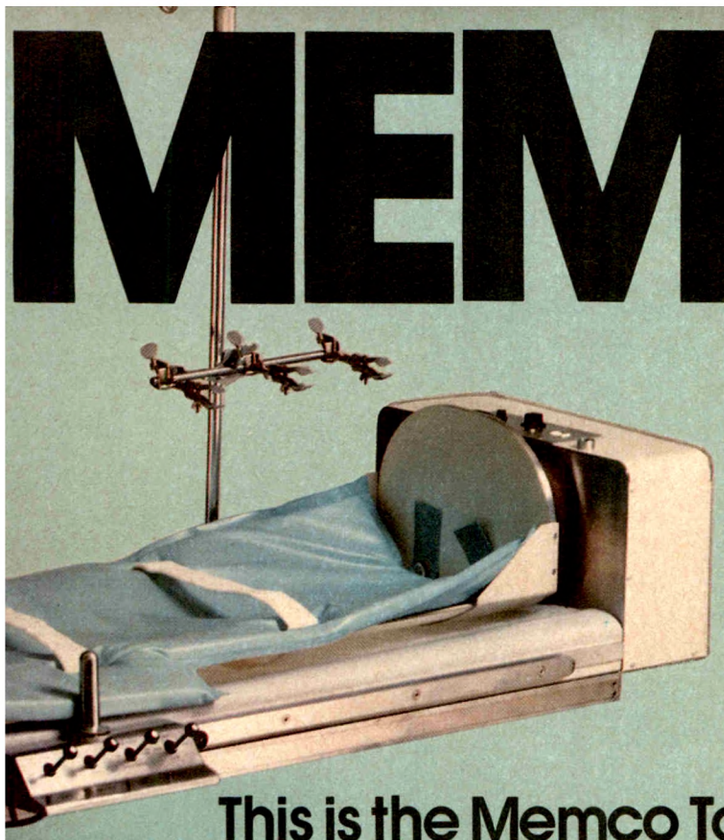
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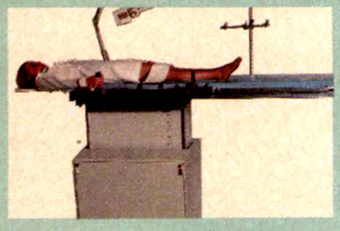


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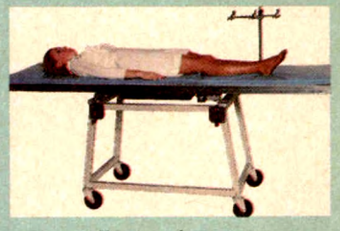
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PRECAUTIONS: Administer with caution and adjust to the requirements of the individual patient. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
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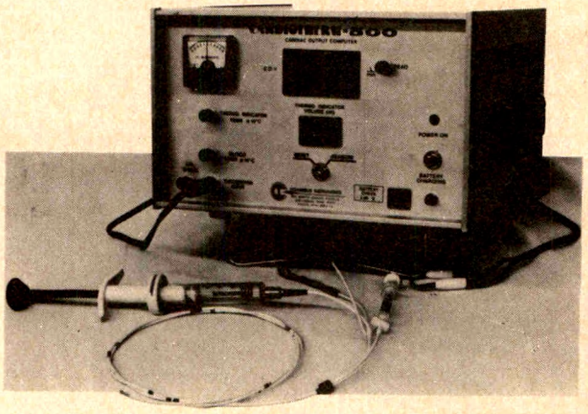


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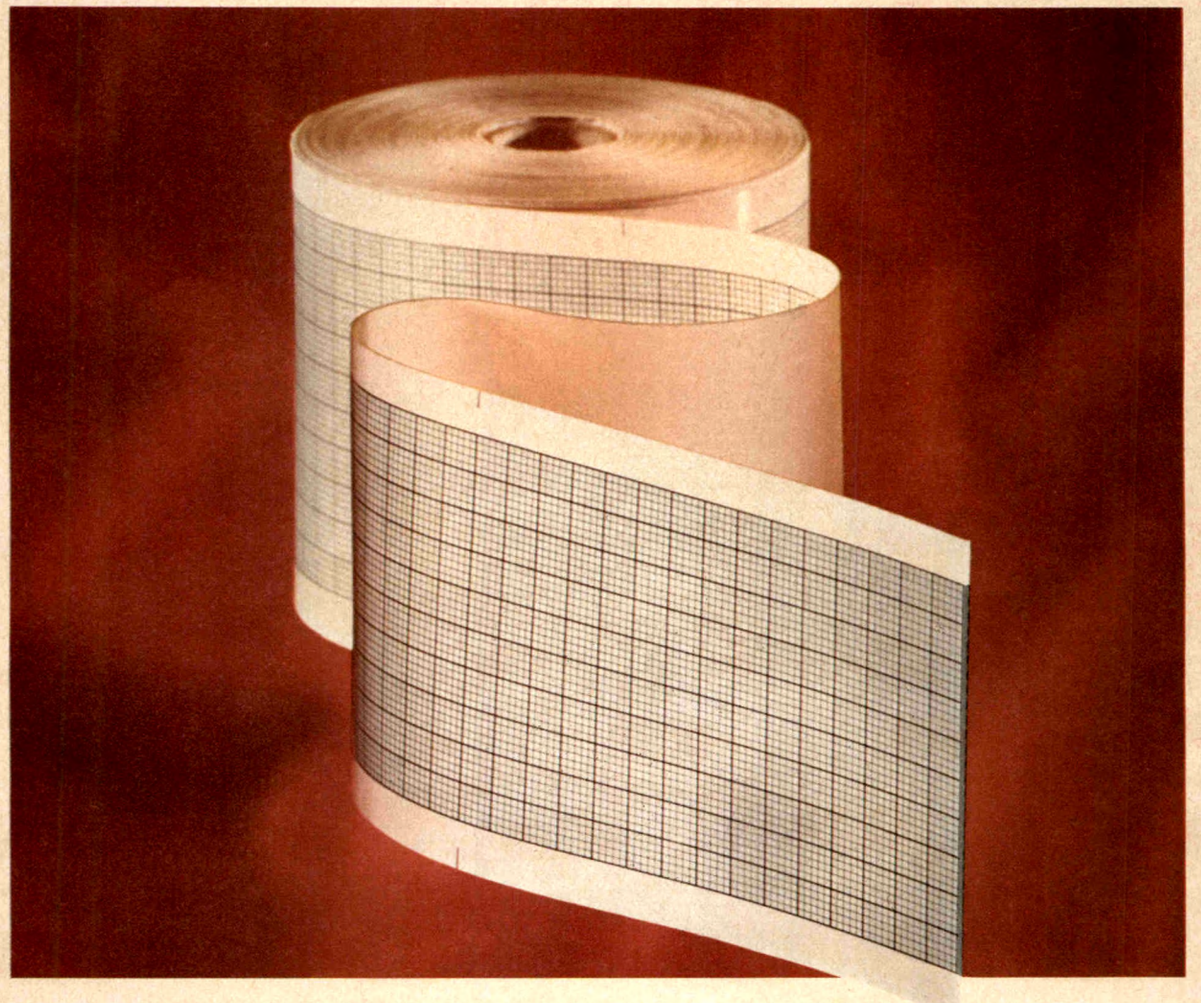


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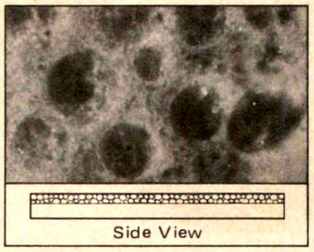
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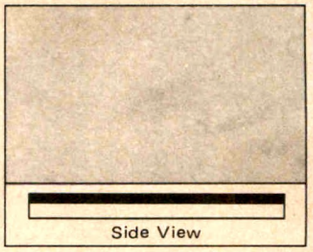
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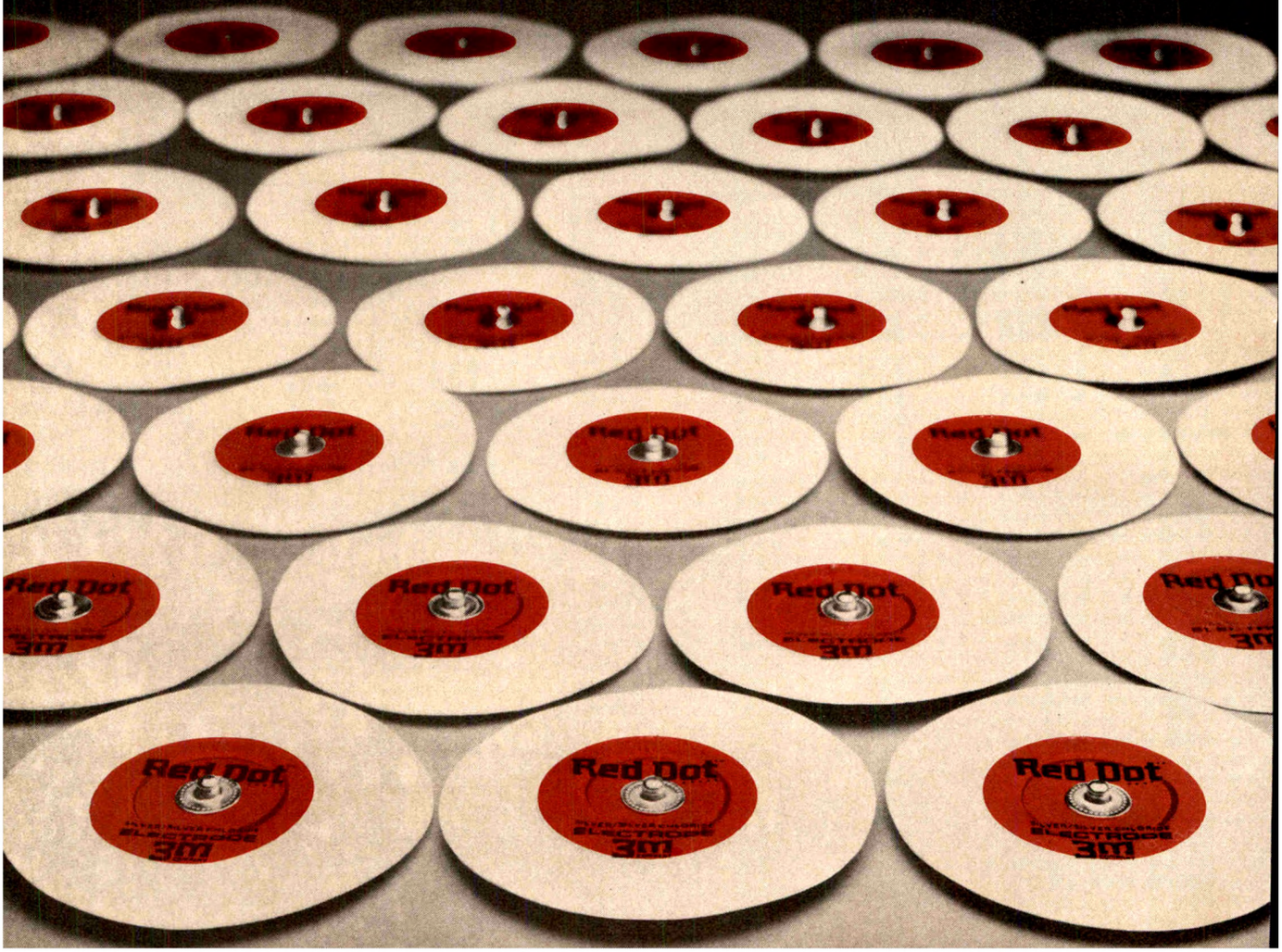
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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

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improve exercise tolerance

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(dipyridamole) Tablets of 25 mg

non-nitrate
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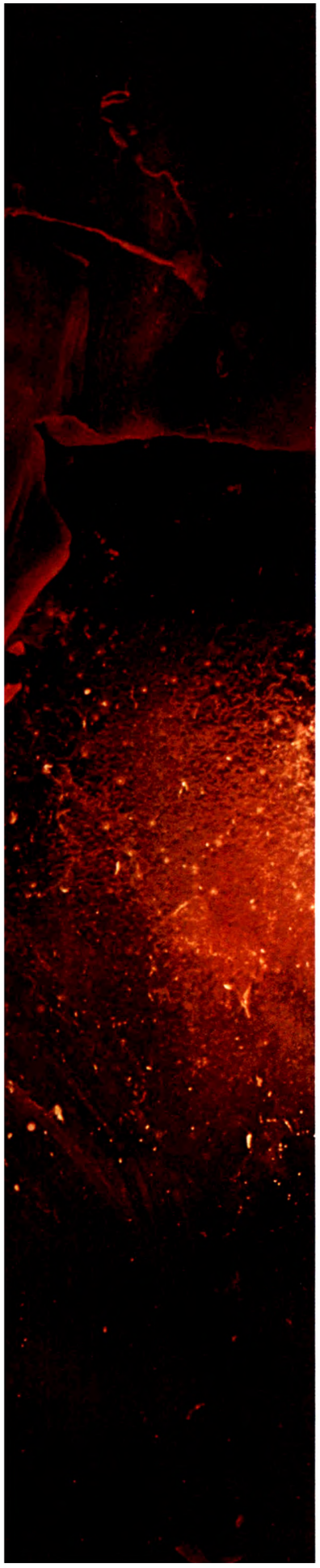


A Broken Heart

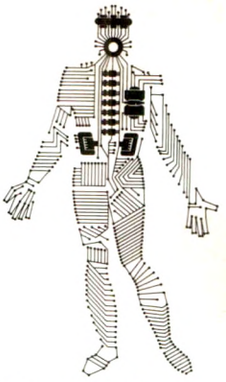
It can start with a little high blood pressure

Infarction with rupture of the wall in the left ventricle of man, 66, with mild hypertension. Blood clot in pericardial sac. Postmortem.

Photographed exclusively for Boehringer Ingelheim by Lennart Nilsson.



Reach for normal blood pressure



In mild to moderate hypertension

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Catapres can make a diuretic look good.

When more than a diuretic is needed, adding Catapres usually lowers blood pressure more.[1]

You can add Catapres to Catapres to get pressure down near normal.

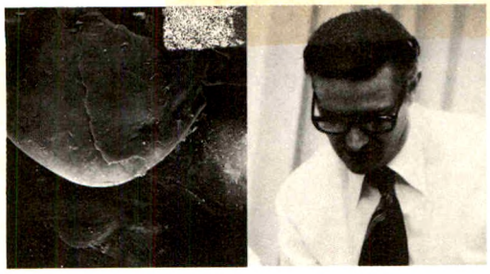
Wide therapeutic dosage range—0.2 mg to 2.4 mg* daily. Catapres may be all you need to reach near-normal levels.

*Doses as high as this have rarely been employed.

Catapres usually doesn't add a lot of problems.

The most common side effects—dry mouth, drowsiness, sedation—generally tend to diminish with time. When stopping Catapres, reduce dosage gradually over two to four days to avoid a possible rapid rise in pressure.

Please see next page of advertisement for a brief summary of the prescribing information including precautions, warnings, and adverse reactions.



Hypertension through the lens of Lennart Nilsson. The photographic genius of Lennart Nilsson has revealed extraordinary details of the human organism. Now, Boehringer Ingelheim has commissioned an exclusive series of photographs by Nilsson depicting hypertensive damage. This series, presented in the interest of continuing medical education, vividly records the progression of an insidious disease.

In mild to moderate hypertension

The Catapres Potential: blood pressure not just down, but down near normal

Catapres® Tablets of 0.1 and 0.2 mg
(clonidine HCl)

Start with Catapres when a diuretic is wrong for your patient

Add Catapres when a diuretic alone doesn't let you reach near-normal pressure

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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Reference: 1. Data on file at Boehringer Ingelheim Ltd.

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LETTERS TO THE EDITOR

CORONARY BYPASS SURGERY AFTER RENAL TRANSPLANTATION

Beauchamp et al.[1] suggested that their three cases are the first reported in which aortocoronary bypass surgery was successfully performed in patients with renal transplantation. In their addendum they do cite the prior report of Lamberti et al.[2] on cardiac surgery in patients with renal dialysis or transplantation.

In 1975, our group[3] described a patient with renal transplantation who had Prinzmetal's angina. After coronary arteriography revealed a severe constriction of the proximal part of the anterior descending artery, aortocoronary bypass surgery was performed. The patient was actually operated on in November 1971. This note is meant to clarify the statement of Beauchamp et al. and to underline that a more thorough search of the literature often shows that the "first" case is not really first.

F. K. Nakhjavan, MD, FACC
Cardiac Hemodynamics Unit
Albert Einstein Medical Center and
Department of Medicine
Temple Medical School
Philadelphia, Pennsylvania

References

1. **Beauchamp GD, Sharma JN, Crouch T, et al:** Coronary bypass surgery after renal transplantation. Am J Cardiol 37:1107–1110, 1976
2. **Lamberti JJ, Cohn LH, Collins JJ Jr:** Cardiac surgery in patients undergoing renal dialysis or transplantation. Ann Thorac Surg 19:135–141, 1975
3. **Nakhjavan FK, Kahn D, Rosenbaum J, et al:** Aortocoronary vein graft surgery in a cadaver kidney transplant recipient. Arch Intern Med 135:1511–1513, 1975

REPLY

We submitted our final revision of the article describing three patients with renal transplantation who underwent successful coronary bypass surgery on August 20, 1975. Dr. Nakhjavan's article did not appear until 3 months later, November 1975, and was therefore not included in our references. The purpose of our article was not to describe a "first case." The remainder of our discussion outlines the various factors we considered before recommending coronary bypass surgery to our three patients.

Gary D. Beauchamp, MD
Kansas City, Missouri

CARDIOSELECTIVE BETA BLOCKADE

In their study of the efficacy of intravenously administered tolamolol in the treatment of cardiac arrhythmias, Amsterdam et al.[1] found no deterioration of respiratory function in six patients with chronic obstructive pulmonary disease, and they stress the value of cardioselective beta blockade in such patients. Although their experience is encouraging, it is well known that the distinction between myocardial and bronchial beta receptors is blurred,[2] and tolamolol, like other "cardioselective" beta blocking agents, has produced bronchospasm in susceptible patients. In a study of the efficacy of this drug, taken orally, in the control of angina,[3] bronchospasm was a complication in 1 of 14 patients with no known airways disease. In this instance, the disability produced was minor and disappeared with discontinuation of the drug. Nevertheless, although the benefits of reducing the heart rate as described by Amsterdam et al. may outweigh the risk of inducing bronchospasm, caution should be exercised when using the drug in patients with a history of reversible airways obstruction.

Adrian Williams, MB, MRCP
Cardiothoracic Institute
University of London
London, England

References

1. **Amsterdam EA, Lee G, Morrison S, et al:** Efficacy of cardioselective beta adrenergic blockade with intravenously administered tolamolol in the treatment of cardiac arrhythmias. Am J Cardiol 38: 195–199, 1976
2. **MacDonald AG, McNeil RS:** A comparison of the effect on airway resistance of a new beta blocking drug, ICI 50, 172 and propranolol. Br J Anaesth 40: 508, 1968
3. **Williams A, Holt MC:** An assessment of the anti-anginal effect of tolamolol, a new beta blocking agent. J Int Med Res 3: 399–406, 1975

REPLY

We fully agree that cardioselective beta adrenergic blockade is relative, not absolute, and that it is essential that caution be exercised in its application in patients with bronchospastic disease. However, cardioselective beta adrenergic blockade does generally inhibit cardiac beta (beta-1) receptors to a considerably greater degree than bronchial beta (beta-2) receptors. Steen et al.[1] demonstrated in a double-blind crossover study of 15 patients with obstructive airways disease that propranolol had nine times the effect of tolamolol in reducing airways conductance in doses equipotent in inhibiting maximal heart rate during stress.

Cardioselectivity can thus permit the benefits of beta adrenergic blockade, when indicated, to many patients with bronchospastic disease in whom propranolol would be precluded. This is exemplified by our study in which no impairment of respiratory function was evident in the six patients with obstructive pulmonary disease during effective tolamolol therapy for supraventricular tachyarrhythmias. On the other hand, experience such as that cited by Williams indicates that the degree of inhibition of bronchial beta receptors effected by a cardioselective beta blocking agent may be sufficient to produce clinically significant bronchospasm. Thus, in the latter condition, safe and effective application of cardioselective beta blockade is predicated on an awareness of potential hazards and caution in its use.

Ezra A. Amsterdam, MD, FACC
Coronary Care Unit
Dean T. Mason, MD, FACC
Section of Cardiovascular Medicine
School of Medicine
University of California, Davis
Davis, California

Reference

1. **Steen SN, Clifton JF, Ziment I, et al:** Double-blind study of tolomolol and propranolol in patients with bronchospastic disease. In, Clinical Experiences With Tolamolol, A Cardioselective Beta Blocking Agent. Amsterdam, Excerpta Medica, 1976, p 48–54

VENTRICULAR ECTOPY IN HEALTHY SUBJECTS

In their clinical study of 25 cases, Kennedy and Underhill[1] hint that a new clinical syndrome of frequent complex ventricular ectopy occurs in apparently healthy subjects. Unfortunately, the noninvasive clinical method that could have been performed in each subject was not performed, and this lack detracts from their conclusions. The performance of an echocardiogram, of the M mode or cross-sectional type, or both, to rule out mitral valve prolapse would have added a great deal. Without this study we are left with the possibility that some of their subjects had silent mitral valve prolapse, which is known to be associated with many of the disturbing arrhythmias they described.

Minor ventricular asynergy might have been assessed without the use of left ventriculography and coronary arteriography by the performance of noninvasive gated blood pool isotopic studies. Such studies produce very little risk to the patient and would appear to be mandatory in an investigation of this type. This article certainly provides food for thought and once again emphasizes the ineffectiveness of our present pharmacologic agents and the fact that many of these arrhythmias are not necessarily being treated.

It would be of interest for the authors to investigate all family members and relatives of these 25 patients to ascertain the possible presence of familial or genetic traits, episodes of sudden death or pathologic confirmation in old records.

Joseph P. Liss, Jr., MD, FACC
Exercise Laboratory
Cardiac Rehabilitation
St. Francis Hospital
Hartford, Connecticut
and
Department of Medicine
University of Connecticut
School of Medicine
Farmington, Connecticut

References

1. **Kennedy HL, Underhill SJ:** Frequent complex ventricular ectopy in apparently healthy subjects. A clinical study of 25 cases. Am J Cardiol 38: 141–148, 1976

REPLY

It is possible that a certain segment of the cohort identified as apparently healthy subjects with frequent or complex ventricular ectopy could have had silent mitral valve prolapse syndrome. As stated under Methods, vectorcardiographic and echocardiographic examination were unavailable in Bellingham, Washington during the evaluation of some subjects, and the possibility of silent prolapse exists for 12 of 13 subjects (1 subject was found to have a normal left ventricular angiogram) identified in that community. Of the remaining 12 subjects of the initial case series report, as well as an additional 17 subjects since identified in Baltimore, Maryland, all have demonstrated normal M mode echocardiographic dimensions and mitral valve motion either during the initial evaluation or at follow-up examination. A normal echocardiographic examination is now requisite for inclusion of such subjects in the cohort longitudinal study. Furthermore, of 15 of 29 subjects of the Baltimore cohort studied with cardiac catheterization and angiography performed after obtaining informed consent, all had normal left ventricular angiograms without evidence of mitral valve prolapse.

The recommendation for noninvasive isotopic gated blood pool studies is timely, and these studies are being sought at annual reexamination in all cohort subjects, particularly those not studied with cardiac catheterization and angiography.

Detailed meticulous histories to date have not disclosed evidence of identifiable familial or genetic traits in the immediate families of the cohort subjects. Sudden death has occurred in one sibling of two cohort subjects and in the father of one cohort subject as ascertained by history. Similarly, preliminary electrocardiographic data from siblings of cohort subjects do not suggest that familial factors are operative. Nevertheless, these variables cannot be conclusively defined or appreciated until the sample cohort enlarges and comparisons with case controls are established. The latter efforts are now in progress.

Much additional work and investigation is required to clarify the clinical syndrome of asymptomatic frequent complex ventricular ectopy in apparently healthy subjects, but the premise that such subjects exist in the general population seems warranted.

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EXERCISE TESTING AND CORONARY ARTERIOGRAPHY

I read with interest the three editorials regarding coronary arteriography in the October 1976 issue of the Journal.[1–3] The editorial by Pichard[1] was refreshing because of its logical, clear, concise and humanistic approach to the pandemic of coronary artery disease. I was happy to see, in the editorial on selection of patients, that Leachman[2] considers shortness of breath an anginal equivalent. We have had at times a great deal of difficulty in explaining this to physicians as well as to patients. I very much agree with him that the exercise electrocardiogram "is not the perfect answer but it is the only tool we have now for making some reasonably noninvasive selection of patients at risk." We are now using the radioisotope thallium-201 in association with the exercise test and, to date, have found this procedure rewarding. The development of other noninvasive techniques, particularly cross-sectional echocardiography, is encouraging.

Gulotta,[3] in his editorial, very nicely demonstrates that exercise electrocardiography, "when performed carefully and interpreted properly" (and I am sure he means not just the S-T segment response but also the blood pressure and heart rate response, signs, symptoms, auscultatory findings, clinical history and physical examination), "does identify patients who are at high risk of having a major coronary event." Exercise electrocardiography is obviously not a panacea but appears to be the best noninvasive predictor of coronary events that we have and provides a quantitative capability that justifies coronary arteriography.

The addition of thallium-201 imaging, which is known to increase the sensitivity and specificity of exercise electrocardiography in relation to the detection of coronary artery disease, should encourage physicians to use this noninvasive predictor of coronary events. Such noninvasive testing often allows the physician to justify, both to himself and to the pa-

tient, the minor risk that is involved in modern coronary arteriography.

The only point that I believe these editorials omitted is that exercise electrocardiography performed early in the postmyocardial infarction convalescent stage may isolate a subset of high risk patients who should undergo coronary arteriography. With these anatomic and physiologic data at hand, the physician can then provide more rational advice on treatment of these patients.

In sum, the Journal should be complimented for this up-to-date and realistic approach to the pandemic of coronary artery disease.

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and
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School of Medicine
Farmington, Connecticut

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STANDARDIZED REGIMEN FOR APPLYING NITROGLYCERIN OINTMENT

An error in the description of the method of applying nitroglycerin ointment (. . . dose of 0.5 to 1.5 inches [1.27 to 3.81 cm] over a 6 by 6 inch [15.24 cm^2 (sic)] area . . .) in the excellent paper by Armstrong et al.[1] is not significant in itself, but it brings to mind the lack of data on guidelines for applying this ointment. Various authors[2–4] describe different techniques of application. To my knowledge no studies have been published that describe how alterations in total dose, area of application and site of application or use of an occlusive dressing affect the rate and completeness of absorption, intensity of effect and duration of action.

It is hoped that pertinent research on these factors will be forthcoming. In the meantime, investigators should consider using a standardized regimen. (Applying the ointment over a 6 by 6 inch area of the abdomen and covering it with a thin sheet of plastic wrap secured at the edges by paper tape is suggested.) This would allow more meaningful comparison of results published from different centers.

H. William Adkison, MD
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Albuquerque, New Mexico

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2. **Taylor WR, Forrester JS, Magnusson P, et al:** Hemodynamic effects of nitroglycerin ointment in congestive heart failure. Am J Cardiol 38:469–473, 1976
3. **Parker JO, Augustine RJ, Barton JR, et al:** Effect of nitroglycerin ointment on the clinical and hemodynamic response to exercise. Am J Cardiol 38:162–166, 1976
4. **Reichek N, Goldstein RE, Redwood DR, et al:** Sustained effects of nitroglycerin ointment in patients with angina pectoris. Circulation 50:348–352, 1974

REPLY

Adkison is correct: Although an area 6 by 6 inches or 6 $inches^2$ when converted to the metric system would correspond to an area of 15.24 cm^2, to be consistent the area in cm should have been expressed as 15.24 by 15.24 cm.

Adkison's request for a standardized regimen of application is indeed well taken and constitutes the reason that in this and a previous study from our institution we have utilized a 6 by 6 inch area, covered with plastic wrap, as outlined by Reichek and co-workers.[1,2] In a recent additional study,[3] an identical area was used for a fixed dose of 2.5 cm of 2 percent ointment but, if more ointment was required to produce a desired hemodynamic effect, it was applied to a second identically sized surface area.

Taylor and co-workers[4] applied the dose of nitroglycerin ointment to a much smaller surface area and covered it with the applicator papers supplied with the medication. Our own experience and that of others suggests that smaller areas may be less propitious for absorption, but this remains to be proved. In a group of 11 normotensive volunteers, the rate of absorption—as measured by the amount of nitroglycerin remaining in the ointment in situ after application—did not vary from that of larger areas when a 3 by 3 inch area was used.[5]

We use the anterior chest or flank because these are the most convenient and available sites for measurements performed in supine patients requiring hemodynamic monitoring. Within individual patients comparable hemodynamic changes occur when either of these sites is used. In the Results section of our study we provided some rationale for the dose utilized; to reiterate, it was in part based on initial hemodynamic measurements, response to intravenously administered nitroglycerin and simple trial and error.

We share Adkison's hopes that further research will help resolve some of the important questions regarding the most effective and appropriate use of this agent. As our Discussion section indicated, answers to these questions should be forthcoming when reliable measurements of blood levels of nitroglycerin become available.

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2. **Reichek N, Goldstein RE, Redwood DR, et al:** Sustained effects of nitroglycerin ointment in patients with angina pectoris. Circulation 50:348–352, 1974
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President's Page: Bethesda Conferences



Dr. Mason

A principal activity of the College in meeting its educational goals is the Bethesda Conference. The College has established such conferences for the exchange of ideas and formulation of policies by recognized authorities concerning matters of patient care and research and training in cardiovascular medicine. Timely subjects of major importance requiring combined expertise for solution are identified by the Bethesda Conference Committee and approved by the Executive Committee. Usually one Conference is scheduled each year; there have been 10 since the first Bethesda Conference in 1965. Leonard S. Dreifus, MD, FACC, of Philadelphia, president-elect of the College, currently serves as chairman of the Bethesda Conference Committee.

The organization of a Bethesda Conference is a formidable undertaking requiring considerable advanced planning by the selected steering committee. After task force topics are established and appropriate members carefully chosen, the participants are invited by the College. All participants attend on an equal basis, with the College serving as host and convener of the forum. There are usually approximately 70 Conference members, including professional specialists in clinical and basic investigation and authorities from industry, government agencies and other concerned organizations. Their overall objective is to reach broad agreement on the issues under deliberation. Before the actual Conference they meet several times in separate task forces to develop preliminary draft reports.

The Conference itself is a continuous two day meeting, initiated by plenary speakers the first half-morning of the initial day. Throughout the remainder of the first day and evening, the various task forces formulate and complete specific position papers. During the night, the completed papers are typed and distributed to the task force members. On the morning of the second day, each task force reconvenes for final approval of its specific position paper. Then all Conference participants reassemble, and during the remainder of the second day hear the reports of the task force chairpersons on the position papers so that agreement on, or modification of, each task force statement is obtained from the entire Conference membership. In this manner, the Bethesda Conference document is finalized for expeditious publication in *The American Journal of Cardiology*.

Bethesda Conferences in action are impressive efficiently functioning operations, and participation in them is a refreshing educational experience. The spirit of each Conference is one of dedicated cooperation, representing the epitomy of volunteerism. No participant receives an honorarium; only expenses are reimbursed. the most recent Conference on Optimal Electrocardiography was held on April 23 and 24. The previous nine Conferences have been on Standards of Physical Fitness of Aircrew (1965); Training Techniques for the Coronary Care Unit (1965); Glossary of Cardiologic Terms Related to Physical Diagnosis and History (1966); The Relation of the Clinical Investigator to the Patient, Pharmaceutical Industry and Federal Agencies (1966); Cardiac and Other Organ Transplantation (1968); Early Care for the Acute Coronary Subject (1969); Development and Introduction of New Cardiovascular Drugs (1974); Cardiovascular Problems Associated with Aviation Safety (1975); and Cardiology Manpower (1975).

It will be possible to hold future Bethesda Conferences in the ideal environment of the College's new Heart House in Bethesda. Conference topics now being considered include the prevention of coronary heart disease, and emergency room and prehospital coronary care. It is clear that, as in the past, the coming Bethesda Conferences will provide an important and effective mechanism for developing concepts that will shape national policy in cardiovascular health care.

Dean T. Mason, MD, FACC
President
American College of Cardiology

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

JULY THROUGH DECEMBER, 1977

1977

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, CA

SEPT. 7–10 — **Core Curriculum: Interpretation and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, directors. Philadelphia Marriott Motor Hotel, Philadelphia, PA

SEPT. 29–30 — **Cardiac Electrophysiology for a Cardiologist.** Borys Surawicz, FACC and Leonard S. Gettes, FACC, directors. Continental Inn, Lexington, KY

OCT. 3–5 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 6–8 — **New Diagnostic and Therapeutic Approaches in Cardiology—1977.** Edmund H. Sonnenblick, FACC and James E. Scheuer, FACC, co-directors. The Plaza, New York, NY

OCT. 10–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 11–14 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

OCT. 13–15 — **New Techniques and Concepts in Cardiology: Pathogenesis and Treatment of Coronary Artery Disease; Sudden Death Without Coronary Disease.** Stephen E. Epstein, FACC, director. The Washington Hilton Hotel, Washington, DC

OCT. 13–15 — **The Clinical Spectrum of Adult Heart Disease.** Jonathan Abrams, FACC, director and Paul T. Cochran, FACC, co-director. University of New Mexico School of Medicine, Basic Medical Sciences Building, Albuquerque, NM

OCT. 21–23 — **Practical Cardiology—1977.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt Hotel, Monterey, CA

NOV. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, co-directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

NOV. 8–10 — **Clinical Perspectives in Valvular and Ischemic Heart Disease.** James T. Mazzara, FACC, director and Richard J. Kennedy, FACC, co-director. St. Vincent's Hospital and Medical Center of New York, New York, NY

NOV. 20–23 — **Coronary, Valvular and Myocardial Heart Diseases: Structure-Function Correlations and Implications for Therapy.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, VA

DEC. 2–4 — **Advances in Heart Disease—1978.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 9–11 — **Tenth Annual Cardiovascular Symposium: Theory and Practice of Cardiology Today.** Henry I. Russek, FACC, director. Americana Hotel, New York, NY

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27th ANNUAL SCIENTIFIC SESSION
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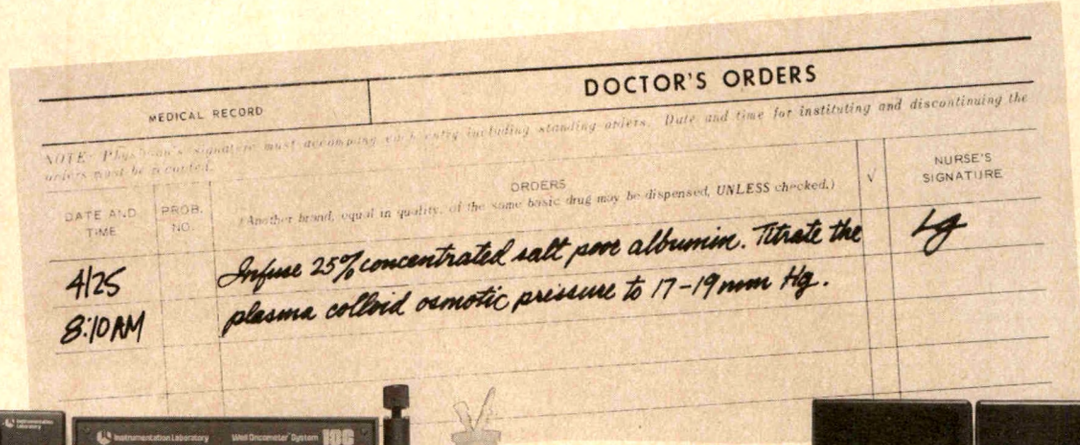
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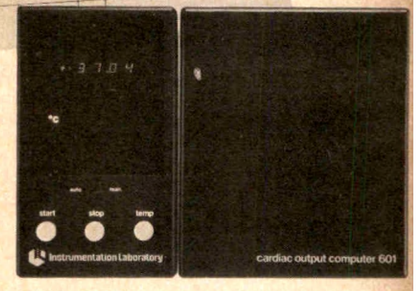
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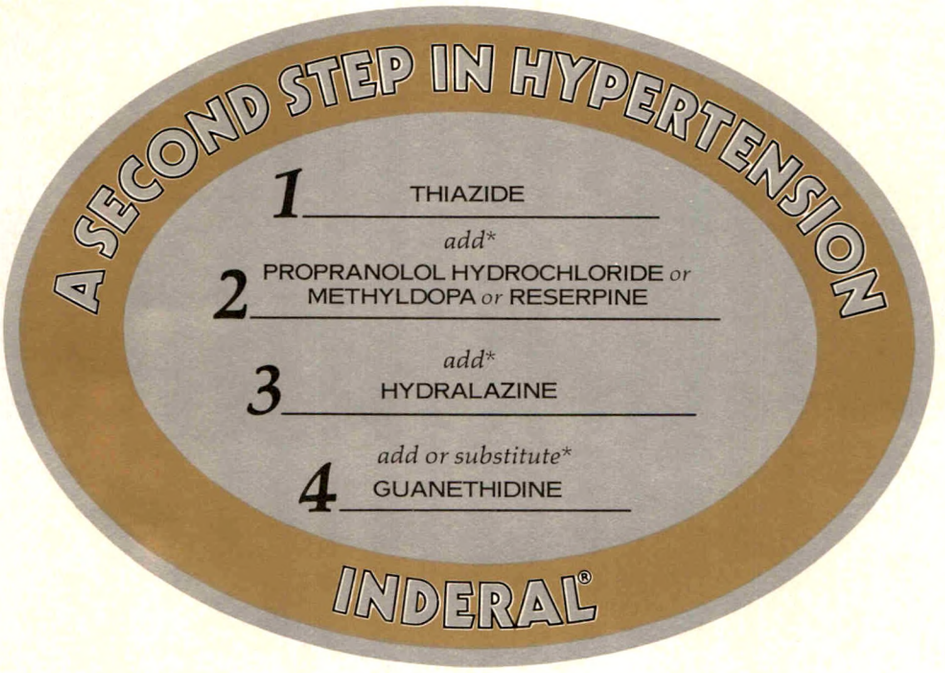
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The Joint National Committee
on Detection, Evaluation, and Treatment of High Blood Pressure
has announced these updated recommendations
for a rational "stepped-care" approach to
the treatment of hypertension
(105-129 mm Hg. diastolic)†



**Presuming inadequate control of blood pressure.*

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BRIEF SUMMARY

(For full prescribing information, see package circular.)

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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

INDICATIONS

Hypertension

INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma, 2) allergic rhinitis during the pollen season, 3) sinus bradycardia and greater than first degree block, 4) cardiogenic shock, 5) right ventricular failure secondary to pulmonary hypertension, 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL, 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely. a) If cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn. b) If tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

HYPERTENSION—*Dosage must be individualized*

The initial dose is 80 mg INDERAL daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved. The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required. The time course of full blood pressure response is variable and may range from a few days to several weeks. INDERAL is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When INDERAL is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

[‡] Moser, M., *et al.* Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, a cooperative study. J.A.M.A. 237:255 (Jan. 17) 1977.

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ISORDIL® CHEWABLE TABLETS 10 mg
(ISOSORBIDE DINITRATE)

for those angina* patients for whom you prefer a chewable isosorbide dinitrate. This higher strength chewable tablet makes increased dosage practical, and the tablet is scored for a lower starting dose and titration of dosage.

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the chewable route, Isordil Chewable Tablets are indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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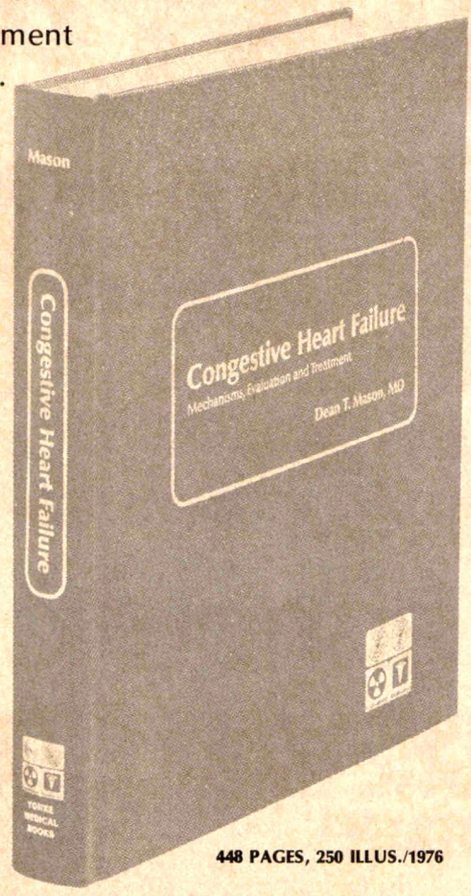
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Congestive Heart Failure

Mechanisms, Evaluation and Treatment

Dean T. Mason, M.D.



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This rare treatment of such a multifaceted subject provides an unusual opportunity for the busy clinician to add to his knowledge in a minimum amount of time. Any area of immediate interest can be rapidly located and as much data as needed can be quickly extracted. The concentration on improved clinical management will be appreciated by every internist, cardiologist, generalist, and any professional involved in cardiovascular medicine.

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis

President, American College of Cardiology President, Western Society for Clinical Research

Member of the American Board of Internal Medicine Cardiovascular Diseases

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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Congestive Heart Failure

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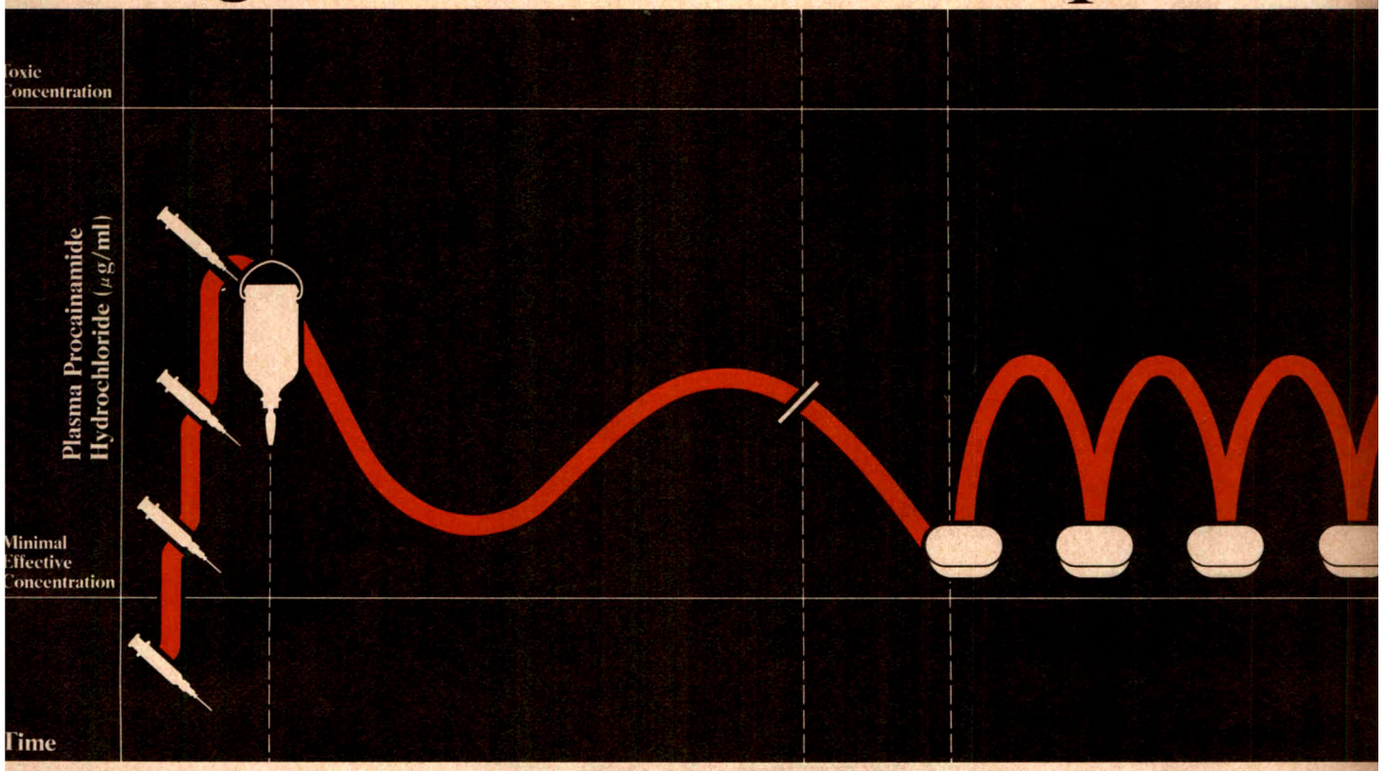
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Dosing continuity throughout the critical care period



I V Injection:
100 mg every 5 minutes until arrhythmia suppressed (up to a maximum dose of 1 gram) to be administered at a rate not exceeding 25 to 50 mg/minute.

I V Infusion:
2-6 mg per minute

(Wyman, MG, Hammersmith L: Amer J Cardiol 33:661-667, 1974)

Pause:
3 or 4 hours before oral regimen begun.

Oral tablets:
50 mg/kg/day

For ventricular arrhythmias, especially following MI

Pronestyl®
Procainamide Hydrochloride

QUIBB

See next page for brief summaries.

RONESTYL® TABLETS
rocainamide Hydrochloride Tablets
RONESTYL® CAPSULES
rocainamide Hydrochloride Capsules U.S.P.

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

ESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide ana-ogue of procaine hydrochloride and is available for oral administration as apsules and veneer-coated tablets providing 250 mg., 375 mg., and 500 mg. rocainamide hydrochloride.

ONTRAINDICATIONS: In patients with myasthenia gravis and where a hyper-ensitivity to procainamide exists; bear in mind cross sensitivity to procaine and elated drugs. Should not be given to patients with complete atrioventricular eart block. Contraindicated in cases of second degree and third degree A-V lock unless an electrical pacemaker is operative.

DMINISTRATION: Should procainamide therapy be continued for any ppreciable period, electrocardiograms should be made occasionally to deter-ine its further need.

RECAUTIONS: Evidence of untoward myocardial response should be care-ully watched for in all patients. In the presence of myocardial damage with trial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial ate is slowed; adequate digitalization reduces but does not abolish this danger. 'entricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur n correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ven-ricular tachycardia has occurred during an occlusive coronary episode or where he use of procainamide may result in additional depression of conduction and entricular asystole or fibrillation as in second degree and third degree A-V lock, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe rganic heart disease and ventricular tachycardia that complete heart block, vhich may be difficult to diagnose, may be present. Since asystole may result if he ventricular rate is significantly slowed without attainment of regular atrio-entricular conduction, procainamide should be stopped and the patient re-valuated.

In the presence of both liver and kidney damage, normal dosage may produce ymptoms of overdosage—principally ventricular tachycardia and severe hypo-ension.

A syndrome resembling lupus erythematosus has been reported with main-enance procainamide therapy. Common symptoms are polyarthralgia, arthritis nd pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis nay also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic nemia, possibly related to this syndrome, have been reported. Measure anti-uclear antibody titers at regular intervals in patients on procainamide for xtended periods of time or in whom symptoms suggestive of lupus-like reaction ppear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, ssess the benefit/risk ratio related to continued procainamide therapy (see oxed Warning). Steroid therapy may be effective if discontinuation of pro-ainamide does not cause remission of symptoms. If the syndrome develops in a atient with recurrent life-threatening arrhythmias not otherwise controllable, teroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions and for full prescribing information.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) and Pronestyl Capsules (Procainamide Hydrochloride Capsules U.S.P.) providing 250 mg., 375 mg., and 500 mg. are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg. and 500 mg. tablets and capsules are also available in bottles of 1000.

PRONESTYL® INJECTION
Procainamide Hydrochloride Injection U.S.P.

DESCRIPTION: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is a sterile aqueous solution providing 100 mg. or 500 mg. procainamide hydrochloride per ml. The 100 mg./ml. potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg./ml. potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

ADMINISTRATION: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

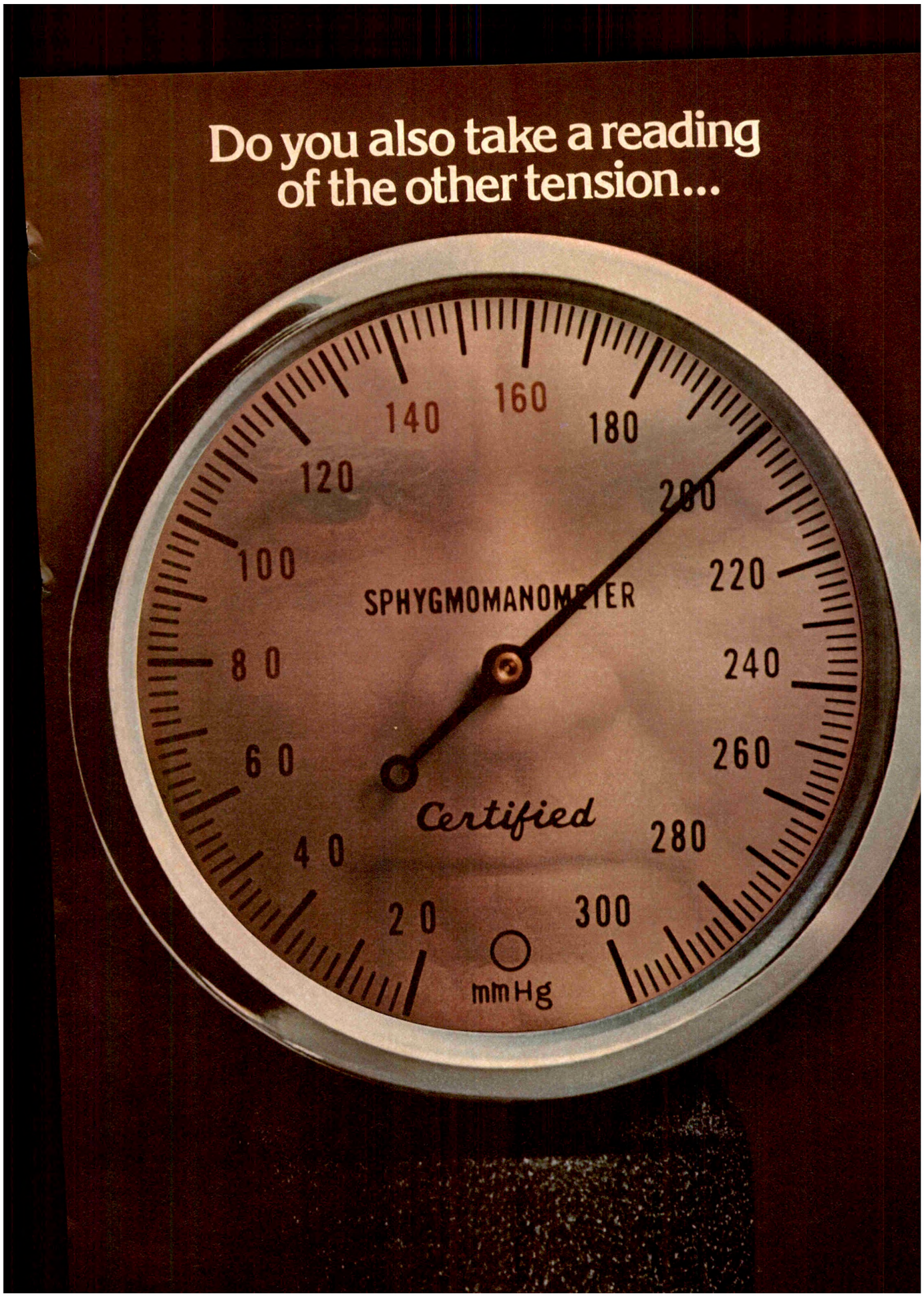
Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

The package insert should be read carefully to become familiar with the recommended dosage for the indicated conditions.

HOW SUPPLIED: Pronestyl Injection (Procainamide Hydrochloride Injection U.S.P.) is available in 10 ml. vials providing 100 mg./ml. and in 2 ml. vials providing 500 mg./ml.

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Excessive psychic tension may well be a distressing problem in your hypertensive patient.

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Equally important: Valium is generally well tolerated and can be used concomitantly with antihypertensive agents, diuretics, cardiac glycosides and most other primary medications. Though drowsiness, ataxia and fatigue are sometimes encountered, these and more serious side effects are rarely a problem.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

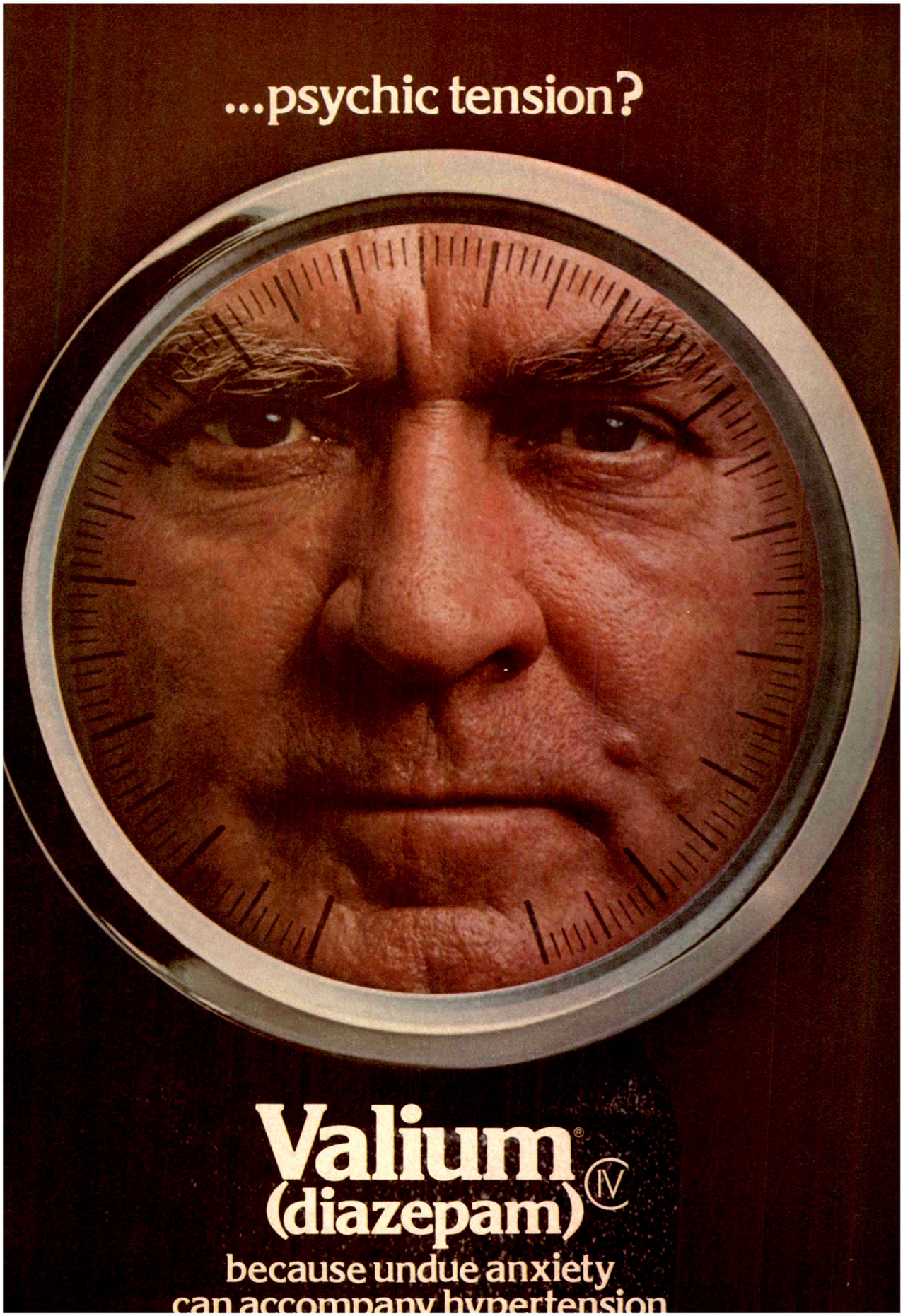
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
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...psychic tension?
Valium®
(diazepam)
because undue anxiety
can accompany hypertension


230
210
190
170
150
130
90
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When choosing a diuretic for day-in-day-out hypertension control with comfortable compliance...

The agent you choose in mild to moderate essential hypertension should offer (1) long-term effectiveness, (2) patient comfort and compliance.

Zaroxolyn offers both.

In one long-term study[1] Zaroxolyn brought moderately elevated (average 161/109 mm Hg) blood pressure down to the range of normotension—and held it there for a year or more.

The investigator noted, "Patient cooperation was surprisingly good for a study of such duration [2½ years]. The once-daily dosage schedule with metolazone [Zaroxolyn] no doubt contributed to patient compliance."

Overall compliance with Zaroxolyn is good—very good. An analysis of controlled clinical studies involving 188 Zaroxolyn patients showed that only eight discontinued therapy because of side effects. That's a discontinuation rate of only 4.3%, and broader clinical experience appears to substantiate this low rate[2]

Zaroxolyn. For long-term control and comfortable compliance in mild to moderate hypertension.

Recommended initial dosage in mild to moderate essential hypertension–2½ to 5 mg once daily

Zaroxolyn®

(metolazone, Pennwalt)

2½-mg, 5-mg and 10-mg tablets

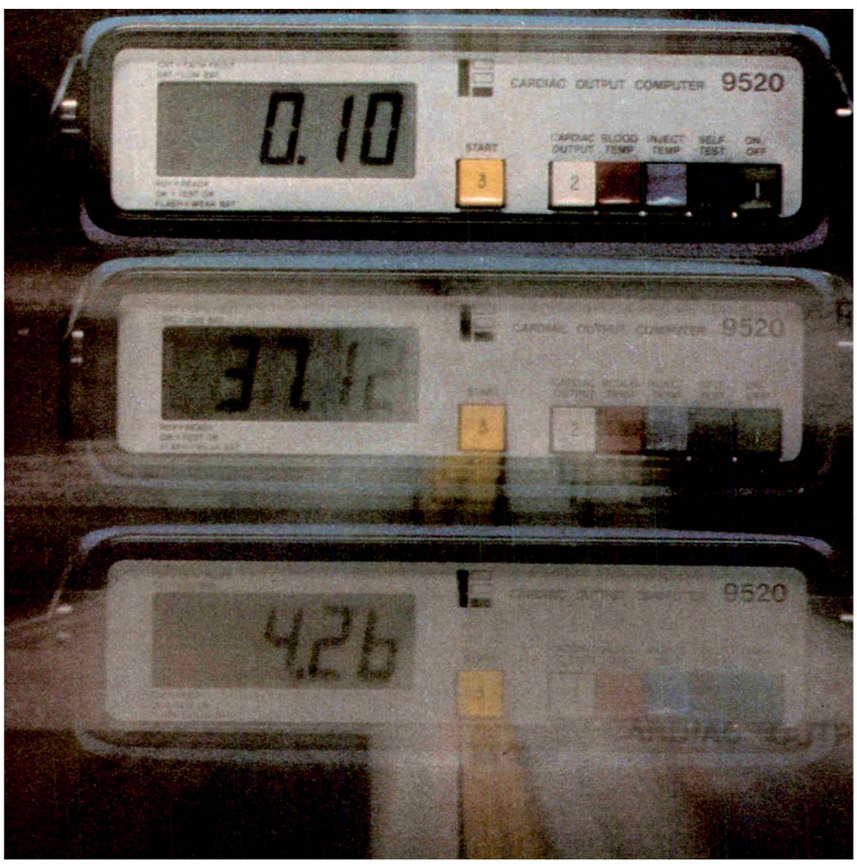
once-daily antihypertensive diuretic

Before prescribing, see complete prescribing information in the package insert, or in PDR, or available from your Pennwalt representative. The following is a brief summary. **Indications:** Zaroxolyn (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease. **Contraindications:** Anuria, hepatic coma or precoma; allergy or sensitivity to Zaroxolyn. Or, as a routine in otherwise healthy pregnant women. **Warnings:** In theory cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may occur. Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When used concurrently with other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to women of childbearing age requires that potential benefits be weighed against possible hazards to the fetus. Zaroxolyn appears in the breast milk. Not for pediatric use. **Precautions:** Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance. These determinations are particularly important when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur in edematous patients in hot weather. **Adverse Reactions:** Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks. **Usual Initial Once-Daily Dosages:** mild to moderate essential hypertension—2½ to 5 mg; edema of cardiac failure—5 to 10 mg; edema of renal disease—5 to 20 mg. Dosage adjustment may be necessary during the course of therapy. **How Supplied:** Tablets, 2½, 5 and 10 mg.

References:
1. Dornfeld L, Kane R: Metolazone in essential hypertension. The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18:** 527-533, 1975.
2. Data on file, Medical Department, Pennwalt Prescription Products.

PENNWALT
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Pharmaceutical Division
Pennwalt Corporation
Rochester, New York 14603

A105


0.10
CARDIAC OUTPUT COMPUTER 9520
START
CARDIAC OUTPUT
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INJECT TEMP
SELF TEST
ON OFF
3
2
1
37.1
9520
4.26

A reputable computer puts its conditions in writing.

You're looking at the only cardiac output computer that offers both automatic body temperature sensing and visual status reporting (VSR).

Automatic sensing improves efficiency through eliminating manual temperature taking.

VSR keeps you informed of the computer's functions by displaying the status of the computer.

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A third generation instrument, our Model 9520 is simple to use, fully portable, and operates with iced or room temperature injectate. Furthermore, it's directly compatible with our new SWAN-GANZ® Thermodilution Catheter.

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When she needed a lithium pacemaker back in 1972, CPI had it ready

CPI was there 4 years ago, when a reliable lithium-powered pacemaker was needed. It was CPI that pioneered the successful use of lithium pulse generators for cardiac pacing. As a result, since 1972, physicians have used CPI pacemakers for effective long-term patient treatment in over 12,000 men, women and children.

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...of the three major pacemaker companies, CPI is No. 1 in lithium.

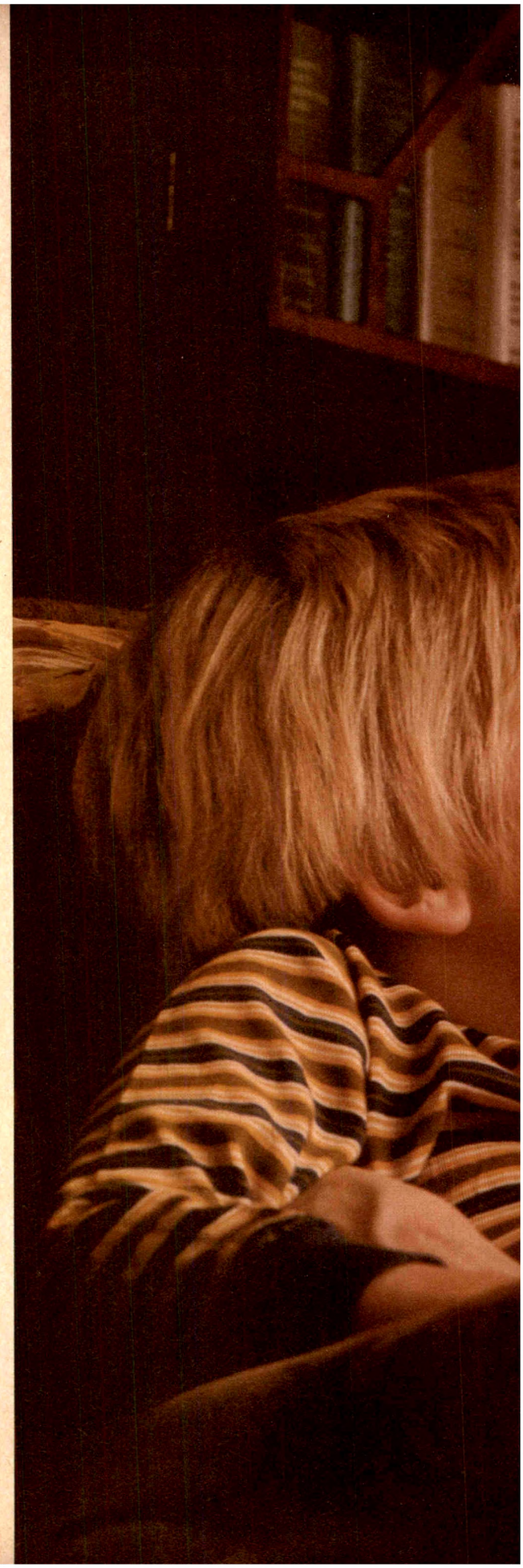




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**Clinical data available upon request*



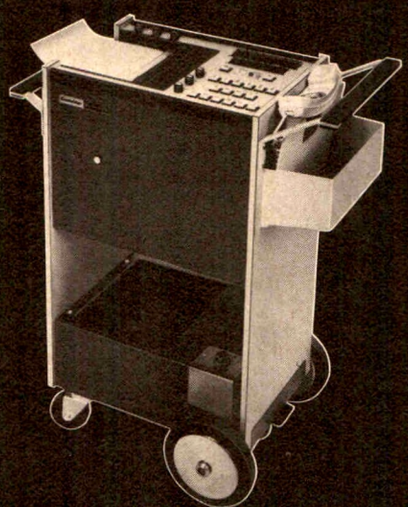

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Dial-a-Diagnosis

All it takes is a phone line, our 3-Channel Electrocardiograph Phone Terminal and one touch of a button.

Electrocardiograph and built-in Computer Phone Terminal you can tie-in with the remote ECG interpretation center of your choice anywhere in the USA and Canada. Fully automated, the Model 3038 brings the convenience of computer aided diagnosis to your location, simply, reliably and at a low cost.



Model 3038 puts you ahead with time-proven advantages other electrocardiographs can't match. State-of-the-art writing precision, with frequency response beyond 250 Hz: a preview feature that cuts paper costs in half, the convenience of drop-in paper loading, the elimination of cutting and mounting, and the versatility of three recording modes (manual, semi-automatic, and fully-automatic).

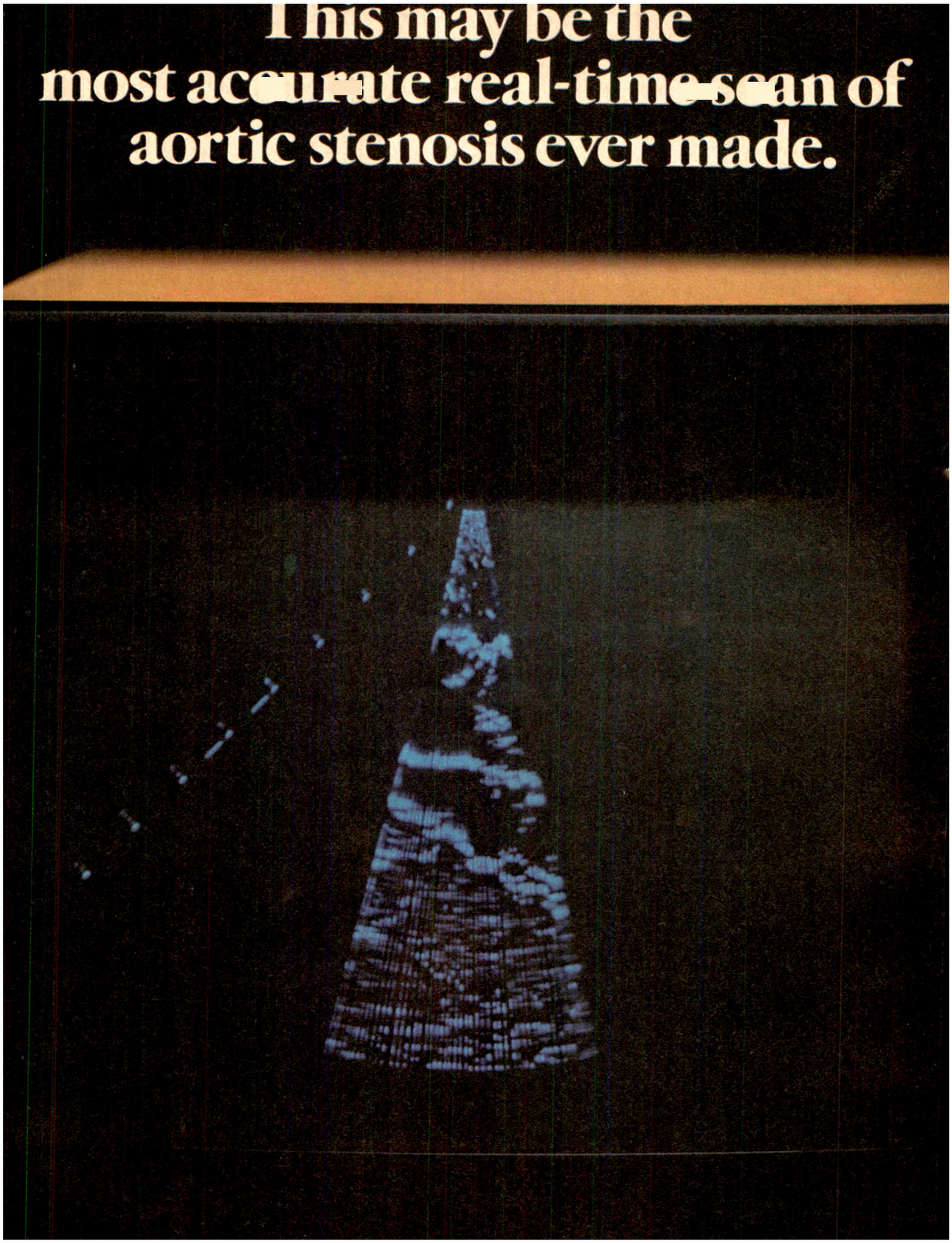
Terminal Option, the Model 3038 puts you ahead even more. Installe in a front-panel compartment, the phone terminal makes the entire diagnostic process as simple as taking a regular ECG.

After connecting patient leads and keying-in patient data, the technician merely previews the ECG ar pushes the PHONE/TRANSMIT button. Automatically, the comput center is dialed, transmission acknowledged, patient ID data ser and ECG lead groups transmitted any format required. Error indicato are built-in, mistakes engineered out. And, while the computer diagnosis is automatically sent to a printer located elsewhere in your facility, the technician is free to mo on. Model 3038 is U.L. approved ar is designed to meet C.S.A. standar Call or write: Cambridge Instrume Company, Inc., 73 Spring Street, Ossining, NY 10562; (914) 941-810 or (212) 931-2100.

Cambridge Instrument Company, Inc.

first in electrocardiography

This may be the most accurate real-time scan of aortic stenosis ever made.



This is why only EkoSector I™ can make it.

As a doctor, you know that your diagnosis can only be as accurate as the information you receive.

What you may not know is that the new EkoSector I from SKI was designed to produce more accurate scans than you've ever seen before.

Real-time cross-sectional scanning with superior resolution.

SKI's patented direct processing method provides distortion-free electronic images and correct, spatially-oriented information concerning the depth relative to the chest wall, lateral relationships and real-time motion of structures.

Some of the clinically reported uses for EkoSector I are: quantitation of mitral stenosis, assessment of aortic stenosis, identification of mitral and tricuspid valves in congenital heart disease, detection of ventricular aneurysms, and localization of ventricular outflow obstructions.

Completely compatible with the Ekoline 20A.

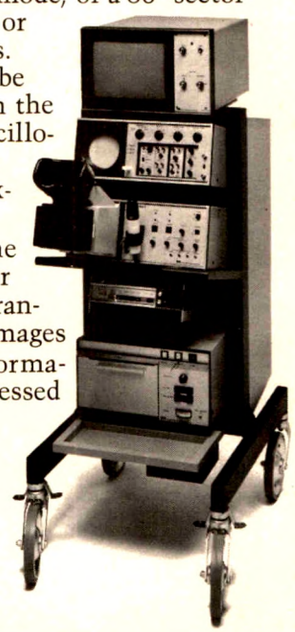
If you already own the world's leading echocardiography unit, you don't need to buy a whole new system for two-dimensional heart scanning.

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A video tape recorder allows you to record M-mode or cross-sectional scans with appropriate verbal comments.

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Or, call 800-538-1556 toll free.
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AJC

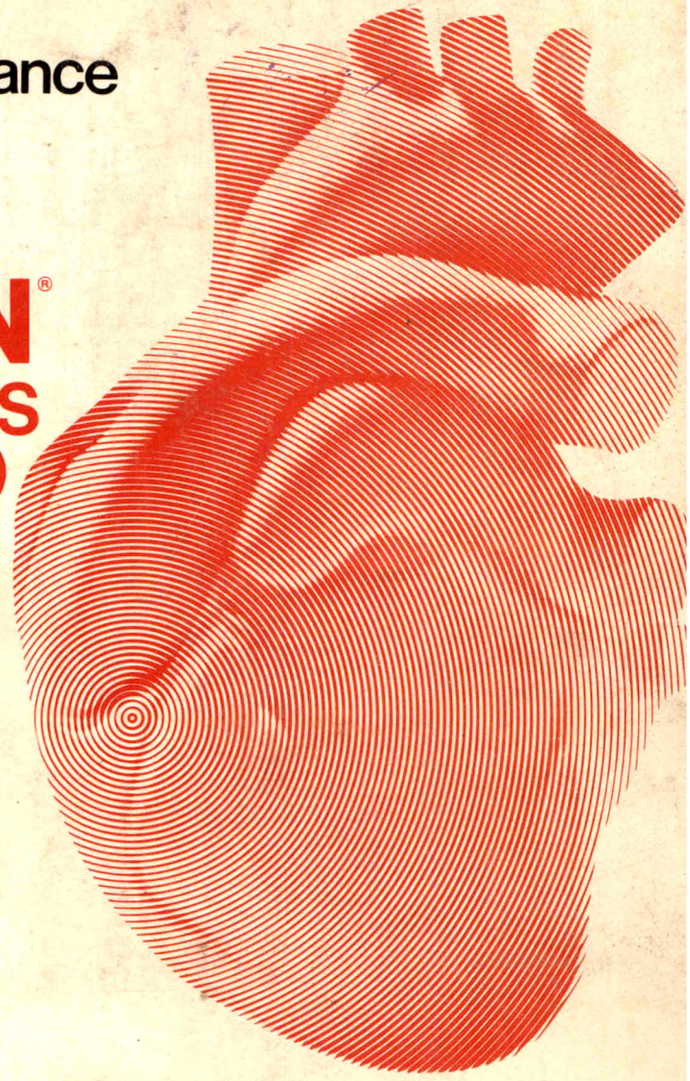
In Canada, mail to Smith Kline Instruments, 300 Laurentien Blvd., St. Laurent, Quebec, Canada. In the United Kingdom, mail to Smith Kline Instrument Co. Ltd., Welwyn Garden City, Hertfordshire, England.

EkoSector I from SKI

The leader in diagnostic ultrasound.

The Pacekeeper™

For the broad spectrum of cardiac arrhythmias broad-range treatment... conversion and maintenance



CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance
- ☐ Full quinidine cardiodynamics
- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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AUGUST 1977

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Coronary Arteritis Due to Mucocutaneous Lymph Node Disease

A Perspective on Exercise Testing in Coronary Artery Disease

Critique on Primary Prevention of Coronary Disease

Call for Abstracts: ACC 27th Annual Scientific Session
Anaheim, California, March 6 to March 9, 1978

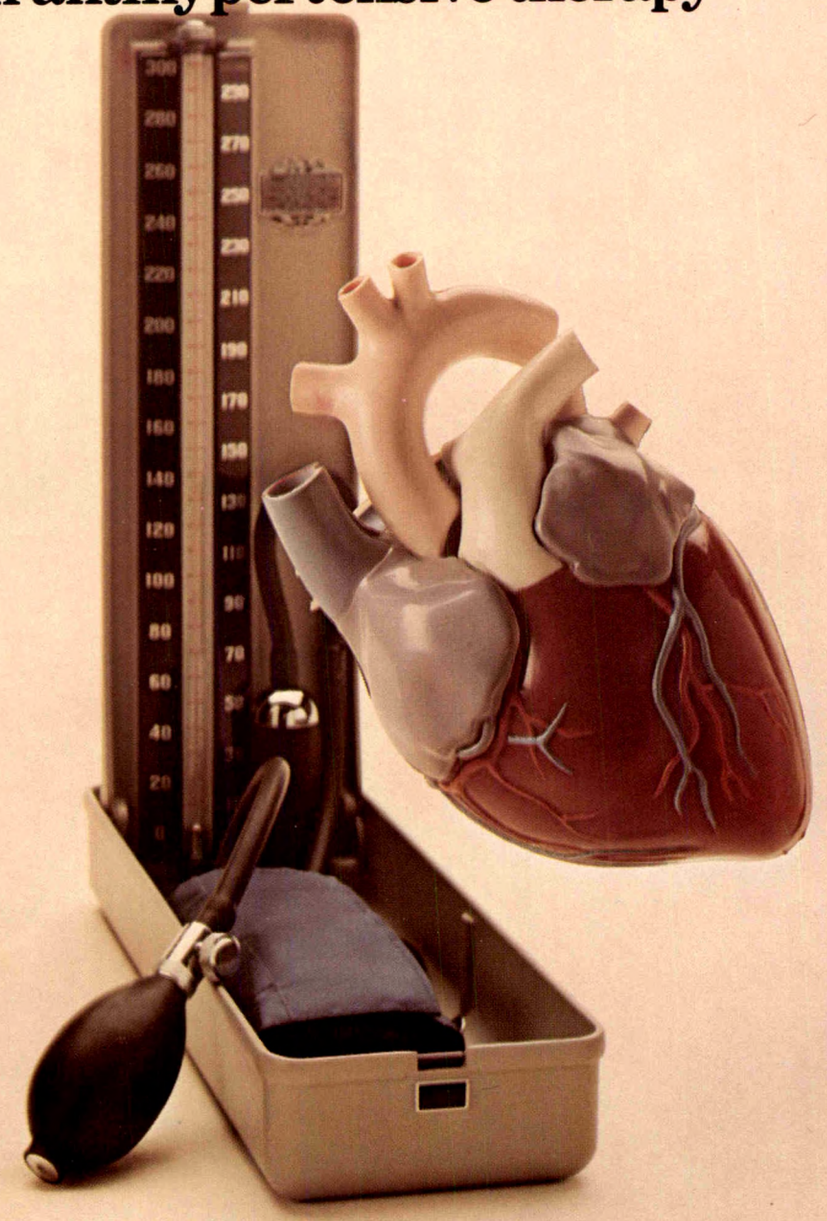
Contents on Page A5

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A YORKE MEDICAL JOURNAL

A Dual Challenge

in antihypertensive therapy



to lower blood pressure effectively...

without compromising existing cardiac output

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

ALDOMET®

(METHYLDOPA | MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function— cardiac output is usually maintained

addendum

MSD MERCK SHARP & DOHME

Some other characteristics of **ALDOMET** (Methyldopa, MSD) for your consideration

ALDOMET usually lowers blood pressure and:

- Usually does not compromise existing renal function
- Infrequently causes symptomatic postural hypotension
- Normal or elevated plasma renin activity may decrease during the course of therapy
- Usually is well tolerated. Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms. However, significant adverse effects due to ALDOMET have been infrequent. (See brief summary for a complete listing of adverse reactions.)

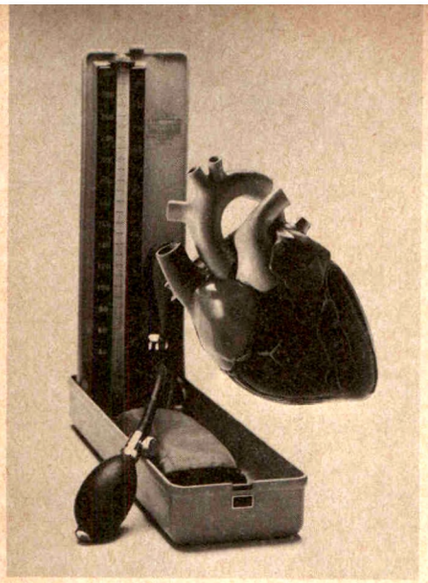
ALDOMET is useful in all degrees of hypertension and offers dosage flexibility with three tablet strengths—the standard 250 mg, the convenient 500 mg, and the 125 mg.

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

MSD MERCK SHARP & DOHME

For a brief summary of prescribing information, please see following page.



in hypertension

ALDOMET®

(METHYLDOPA|MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function– cardiac output is usually maintained

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

J2634R1(707)

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The American Journal of CARDIOLOGY®

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References:

1. Dornfeld L, Kane R: Metolazone in essential hypertension. The long-term clinical efficacy of a new diuretic. *Curr Ther Res* **18:** 527-533, 1975.
2. Data on file, Medical Department, Pennwalt Prescription Products.

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HARTMUT HENNING, HEINRICH R. SCHELBERT, ALBERTO RIGHETTI, WILLIAM L. ASHBURN and ROBERT A. O'ROURKE

Myocardial imaging with technetium (Tc)-99m pyrophosphate and thallium-201 in the same 35 subjects performed within 1 to 5 days after the onset of acute myocardial infarction showed that thallium-201 was more accurate in detecting and localizing acute myocardial infarction and in differentiating between mild, moderate and large infarcts in patients with prior infarction, but did not accurately measure the extent of the acute myocardial infarction. Tc-99m pyrophosphate may fail to identify small infarctions, permits estimation of infarct size in patients with anterior infarcts but underestimates the size of inferior infarcts. With the refinement and new development of imaging techniques, the combined use of "cold" and "hot spot" tracers may allow a more precise characterization of zones of ischemia and infarction and provide information about the perfusion and function of the remaining noninfarcted areas of myocardium.

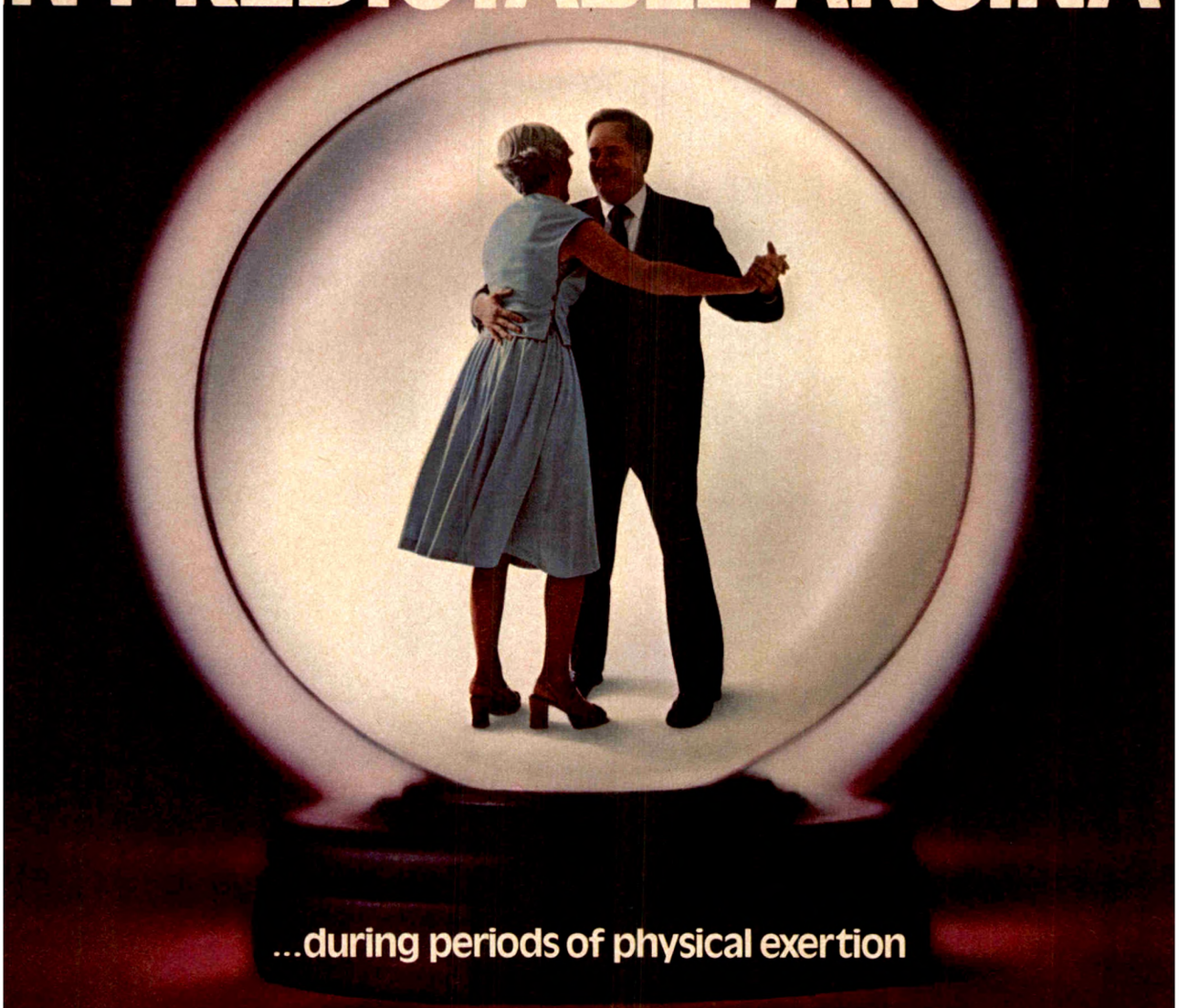
156 **Left Ventricular Function in Patients With Coronary Arteritis Due to Acute Febrile Mucocutaneous Lymph Node Syndrome or Related Diseases**

SOICHIRO KITAMURA, YASUNARU KAWASHIMA, KANJI KAWACHI, MASAOKI FUJINO, TAKAHIRO KOZUKA, TSUyoshi FUJITA and HISAO MANABE

Acute febrile mucocutaneous lymph node syndrome, a specific arteritis of unknown etiology, has an extraordinary tendency to involve the large coronary arteries and can compromise left ventricular function as a process of the disease or as a consequence of coronary arterial involvement. The syndrome is predominant among Japanese children but also appears elsewhere. Coronary arterial aneurysm or occlusion developed in 6 of 12 patients with this disease or with a related coronary arteritis. Four of these six had abnormal hemodynamic changes. In this group regional contraction abnormalities secondary to myocardial infarction and generalized hypokinesia without electrocardiographic evidence of infarction, but probably caused by myocarditis resulting from arteritis, were identified. Aortocoronary bypass grafting was successful in two patients with severe coronary arterial obstruction and myocardial infarction. It is possible that the child with coronary arteritis due to mucocutaneous lymph node syndrome or related diseases may sustain myocardial infarction as an adult or may be found to have mitral regurgitation long after the acute episode has subsided and is almost forgotten or neglected.

Continued on page A12

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Indications: Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

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Adverse reactions seen occasionally: Cutaneous vasodilation with flushg; transient dizziness and weakness as well as other signs of cerebral chemia associated with postural hypotension; individual marked sensivity to the hypotensive effects of nitrates wherein severe responses can ccur even with the usual therapeutic dose (alcohol may enhance this ffect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylholine, histamine and other agents.

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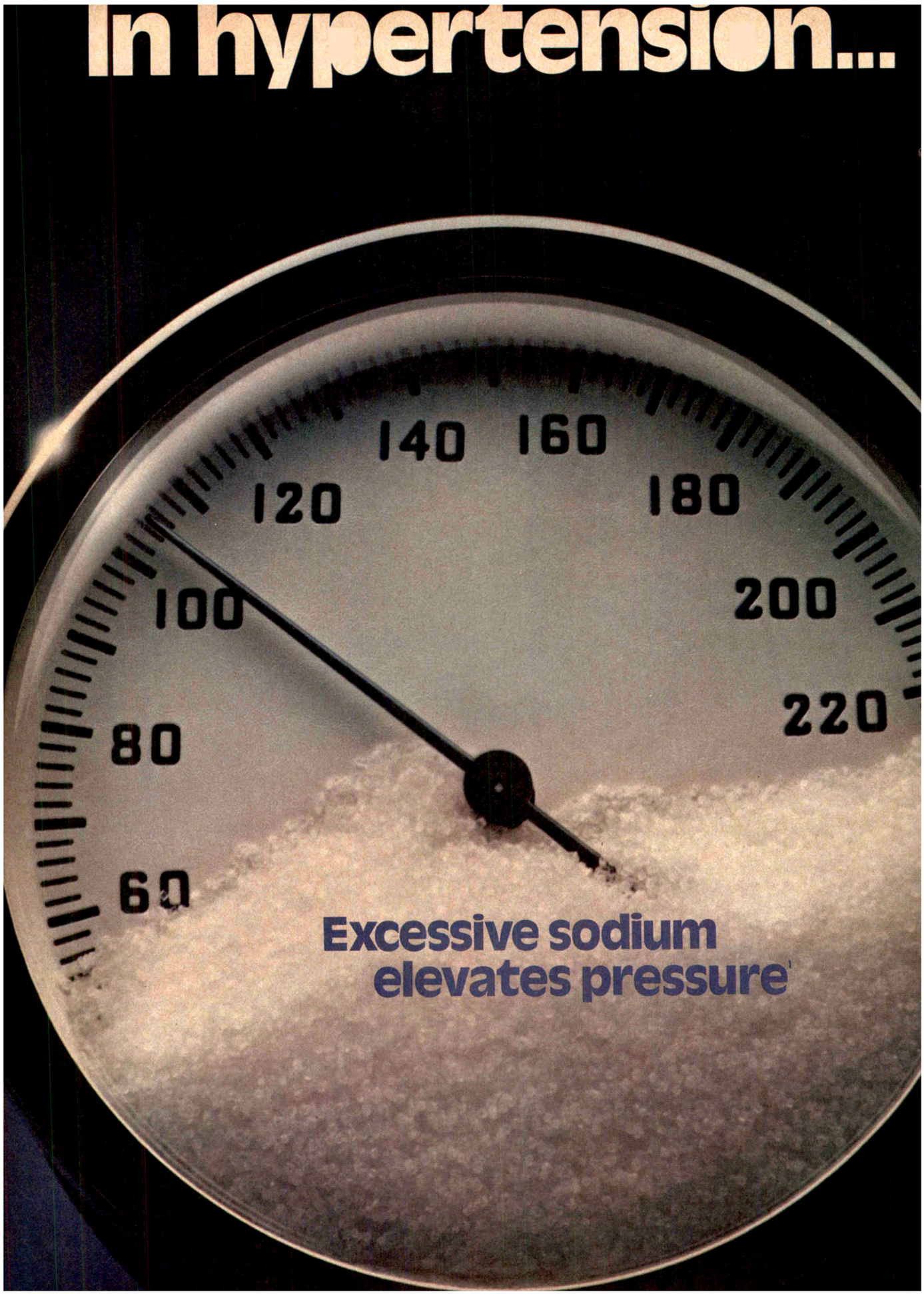
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Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

References:

1. Laragh, J.H. et al.: Vasoconstriction – volume analysis for understanding and treating hypertension: The use of renin and aldosterone profiles, in Hypertension Manual (Laragh, J.H., ed.), New York, Dun-Donnelley, 1974, pp. 824-825. **2.** Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: A Cooperative Study, JAMA 237:255, January 17, 1977.

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165 Angiographic Diagnosis of Mitral Valve Prolapse: Correlation With Echocardiography

ELDON R. SMITH, DAVID B. FRASER, JOHN W. PURDY and ROBERT N. ANDERSON

Angiographic mitral valve prolapse (leaflet bulging) was detected in 43 percent of 336 consecutive subjects selected without regard for their primary cardiac diagnosis. Echocardiographic evidence of mitral valve prolapse was found in 9 (6.4 percent) of 140 subjects, including 6 with a clinical diagnosis of click-murmur syndrome. In the absence of other features of the click-murmur syndrome, angiographic end-systolic bulging of the posterior mitral leaflet scallops should not be considered indicative of pathologic mitral valve function. Echocardiography may be more specific than angiography in providing objective evidence of mitral valve prolapse, although some patients with true prolapse may have no echocardiographic abnormalities.

171 Short- and Long-Term Effects of Digitalis on Resting and Posthandgrip Hemodynamics in Patients With Coronary Artery Disease

ROBERT VOGEL, JOHN FRISCHKNECHT and PETER STEELE

These studies show that the intravenous administration of ouabain in eight patients with coronary artery disease increased the resting left ventricular ejection fraction and decreased resting left ventricular end-diastolic volume index and heart rate without significantly changing resting cardiac index and blood pressure. Handgrip exercise significantly increased heart rate and blood pressure. The short-term oral administration of digoxin improved both resting and exercise volumetric indexes of contractility (left ventricular end-diastolic volume index and ejection fraction). With long-term digoxin administration (after 2 weeks of maintenance therapy) volumetric variables at rest initially improve but later return to control levels, whereas values after exercise continue improved. Resting volumetric hemodynamics return to predigitalization levels in a few days in patients with clinically mild congestive heart failure.

177 Effect of Lidocaine on Escape Rate in Patients With Complete Atrioventricular Block. A. Distal His Bundle Block

VADAKEPAT ARAVINDAKSHAN, CHIEN-SUU KUO and LEONARD S. GETTES

The intravenous administration of lidocaine either did not affect or slowed the ventricular rate by 16 percent or less in 13 of 18 subjects with complete atrioventricular (A-V) block. In the remaining five patients the rate slowed abruptly, suggesting 2:1 or 3:1 exit block. The site of block was distal to the His bundle potential in these five and in eight other patients who did not have exit block. The pacemaker fibers responsible for the ventricular escape rhythm appear insensitive to the effects of lidocaine, suggesting their spontaneous depolarization may be slow channel-dependent. Lidocaine is unsafe to use without prior pacemaker insertion in patients with complete A-V block located distal to the His bundle potential because of the risk of inducing high grade exit block. These results suggest that the antiarrhythmic effect of lidocaine is due more to its ability to depress conduction than to its ability to suppress automaticity.

184 Threshold Behavior of Electrodes in Long-Term Ventricular Pacing

RICHARD M. LUCERI, SEYMOUR FURMAN, PHILIP HURZELER and DORIS J. W. ESCHER

Electrical stimulation threshold measurements of electrodes in 120 patients followed up 5 to 11.3 years and in an additional 297 patients with low output or programmable pacemakers studied 1 month to 4 years after pacemaker implantation show an overall threshold stability up to 11 years after pacemaker implantation in 81 percent of cases. The data support the use of the newer low output pulse generators with increased longevity. However, strict surveillance and noninvasive determinations of threshold when possible are required to detect the remaining 19 percent of patients whose electrical stimulation threshold seems to rise chronically and inexplicably.

Continued on page A17

Time is the test of all things.

1954
1977



BRIEF SUMMARY

Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. May be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.

Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation.

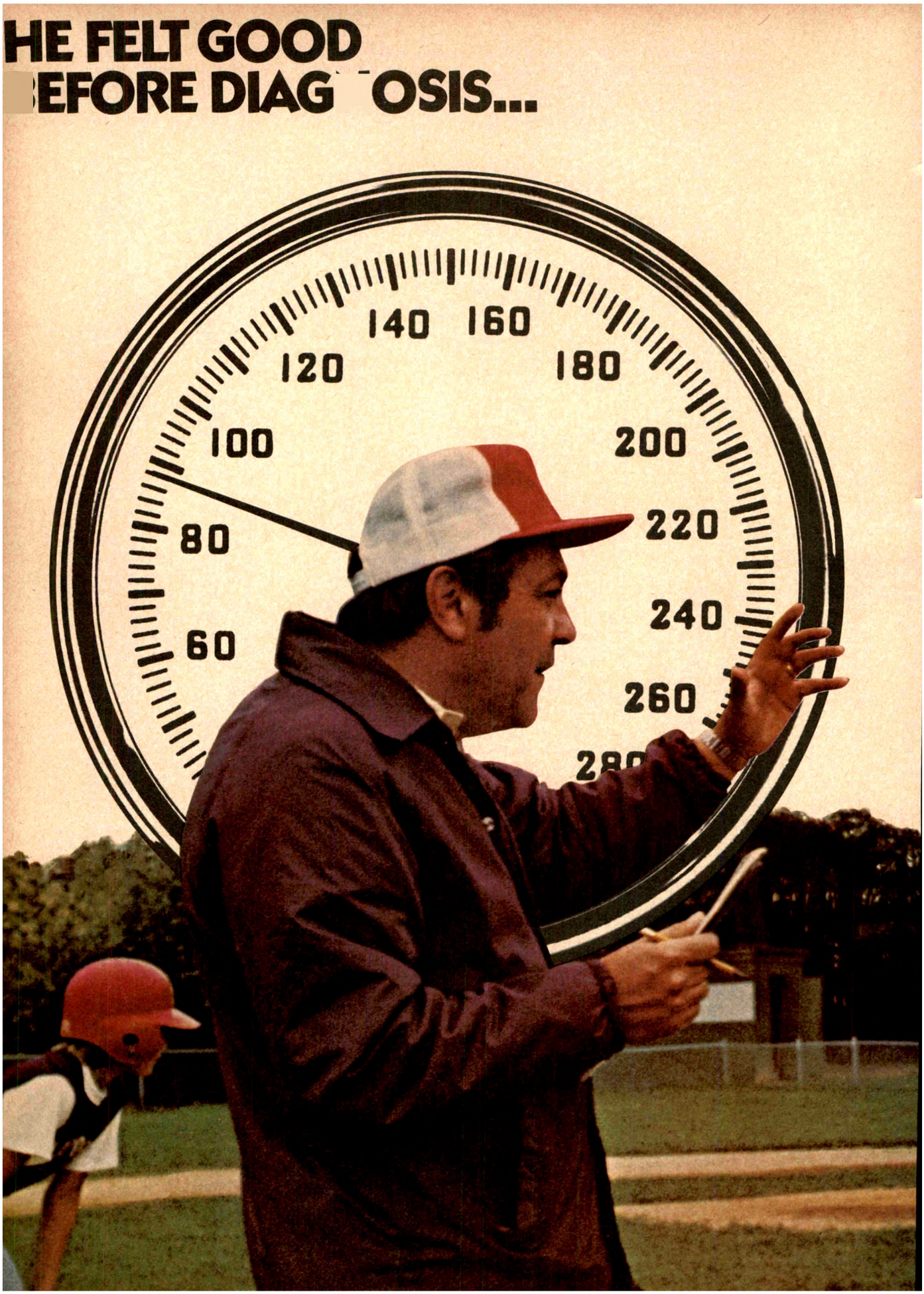
Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The most severe adverse effect is hyperkalemia.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications". Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

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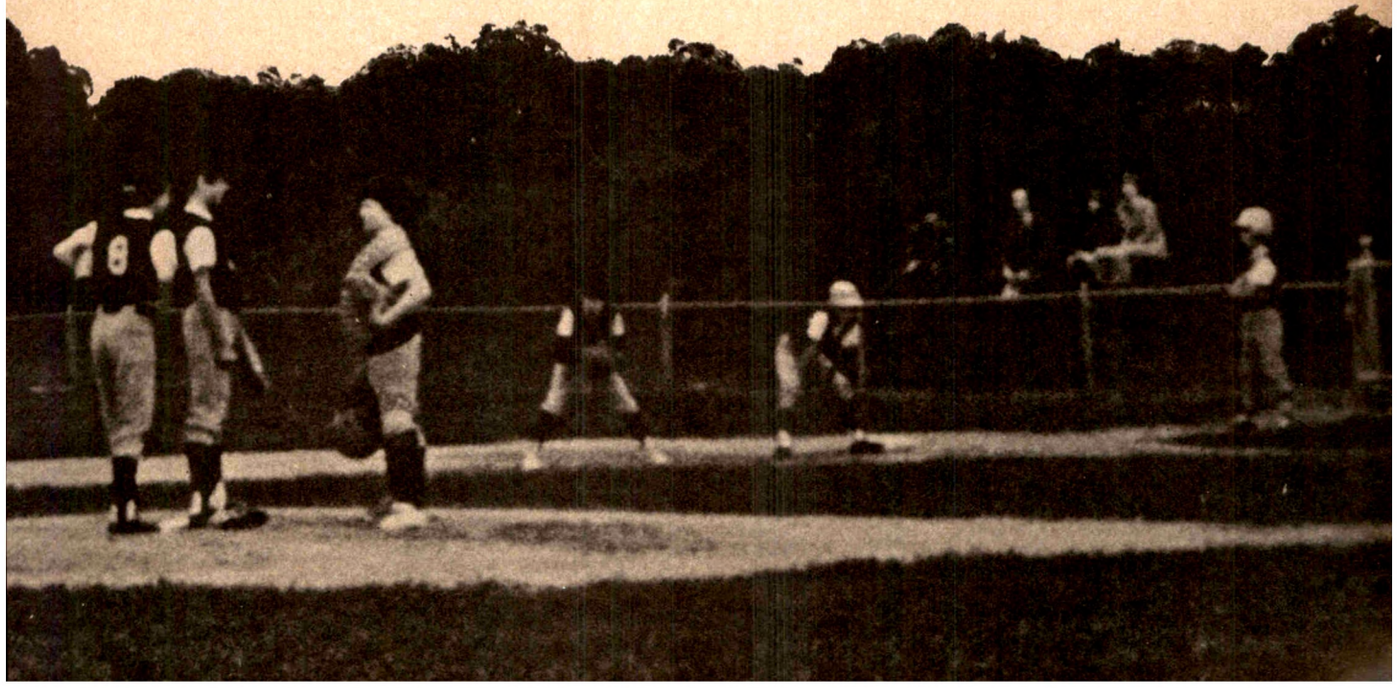
One or two capsules, once or twice daily for maintenance according to the response of the patient. Tedious, expensive K^+ rich diets or potassium salts should not be used unless hypokalemia develops or dietary K^+ intake is markedly impaired.

Serum K^+ and BUN should be checked periodically

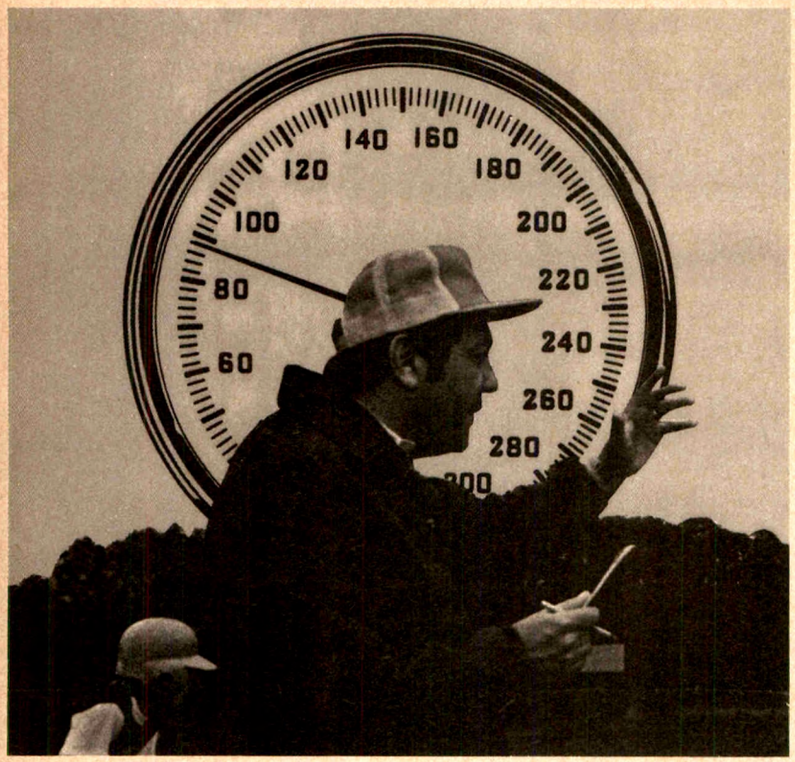
particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Elevated serum potassium levels can occur because of the K^+-sparing effect of triamterene, but they are rare in patients with normal renal function. If hyperkalemia develops, substitute a thiazide alone. Routine use of diuretics in healthy pregnant women is inappropriate.

*Not for initial therapy (see box warning). See next page for indications and brief summary of prescribing information.

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Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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CONTENTS

189 **Ability of Holter Electrocardiographic Recording and Atrial Stimulation to Detect Sinus Nodal Dysfunction in Symptomatic and Asymptomatic Patients With Sinus Bradycardia**

JAMES A. REIFFEL, J. THOMAS BIGGER, Jr., MARVIN CRAMER and DOUGLAS S. REID

Although each was helpful, combined Holter electrocardiographic recording and functional testing (determination of corrected sinus recovery time and estimated sinoatrial conduction time) proved more useful than either alone in detecting sinus nodal dysfunction. Two of eight patients with recognized evidence of sick sinus node syndrome in prereferral electrocardiograms had normal Holter recordings. The results in this study also indicate that the combination of a normal Holter electrocardiogram and normal functional testing, using a corrected sinus recovery time greater than 525 msec or sinoatrial conduction time greater than 120 msec, or both, is strong evidence against the presence of significant sinus nodal dysfunction.

EXPERIMENTAL STUDIES

195 **Imaging of the Inflammatory Response in Ischemic Canine Myocardium With ^{111}Indium-Labeled Leukocytes**

EDWARD S. WEISS, SYED A. AHMED, MATHEW L. THAKUR, MICHAEL J. WELCH, R. EDWARD COLEMAN and BURTON E. SOBEL

This study in dogs demonstrates the value of indium-111-labeled leukocytes in detecting serially and noninvasively leukocytic infiltration associated with acute myocardial infarction. Intravenously administered autologously labeled indium-111 leukocytes accumulated after 72 hours in regions corresponding to myocardial infarcts in dogs with experimentally produced coronary occlusion. The half-life of this radionuclide (67 hours) permits sequential studies for several days without excessive radiation burden. In addition to the detection of myocardial infarction, this technique may also prove useful to detect bacterial endocarditis, myocarditis, pericarditis and other conditions characterized by leukocytic accumulation and infiltration.

200 **Relation Between Progressive Decreases in Regional Coronary Perfusion and Contractile Abnormalities**

VIDYA S. BANKA, MONTY M. BODENHEIMER and RICHARD H. HELFANT

This short-term study in 10 open chest dogs demonstrates that coronary obstruction producing a 25 percent reduction in distal coronary arterial pressure and flow causes no abnormalities in segmental function. But a further reduction in distal coronary arterial pressure and flow to 50 percent of control level results in regional contraction abnormalities and dysfunction manifested by a reduction in total tension development and an increase in segment length. Regional myocardial shortening persists throughout systole, but at a decreased level because tension is maintained during the ejection phase. A 75 percent decrease further aggravates these abnormalities in tension and length and causes the systolic fiber shortening to disappear and to be replaced by a paradoxical systolic expansion manifested by loss of tension during the ejection phase. Total coronary occlusion produced a further decrease in coronary blood flow but no additional short-term abnormalities in contraction.

PEDIATRIC CARDIOLOGY

206 **Systolic Honks in Young Children**

JOEL M. FELNER, SUZANNE HARWOOD, HARRY MOND, WILLIAM PLAUTH, DOROTHY BRINSFIELD and ROBERT C. SCHLANT

Phonocardiography and echocardiography in three children with loud systolic honks showed that the precordial honk results from a prolapse of one or both mitral valve leaflets. The timing of these sounds

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in systole varies with different physiologic or pharmacologic maneuvers and variations in the onset of prolapse are associated with changes in left ventricular end-diastolic dimensions. Patients with this condition should be assured that their disorder is benign and instructed in the prophylaxis of bacterial endocarditis. The precordial honk, like the late systolic mitral murmur and the clicking apical systolic sound, results from a defect of mitral valve support and can be classified as part of the mitral valve prolapse syndrome.

REPORTS ON THERAPY

212 Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and Baseline Characteristics, Including Experience With Medical Treatment

By the Veterans Administration Cooperative Group for the Study of Surgery for Coronary Arterial Occlusive Disease. *Report prepared by Katherine Detre, Herbert Hultgren and Timothy Takaro*

This report on the methods, baseline characteristics and results of medical treatment in a prospective randomized trial of 1,015 patients with occlusive coronary artery disease shows that survival rates of the medically treated group after 2 1/2 years varied widely according to the extent of the cardiac disease. Patients with one or two vessel coronary artery disease and normal ventricular function had a survival rate of more than 90 percent; those with left main coronary artery disease and abnormal ventricular function had a significantly lower survival rate of 65 percent. Preliminary analysis of the data does not indicate that coronary arterial surgery improves survival in patients with single, double or triple vessel coronary artery disease and normal left ventricular function.

226 Coronary Arterial Surgery in Patients With Incapacitating Angina Pectoris and Myxedema

THOMAS D. PAINE , WILLIAM J. ROGERS, WILLIAM A. BAXLEY and RICHARD O. RUSSELL, Jr.

Six patients with severe hypothyroidism safely underwent selective coronary arteriography and quantitative biplane left ventriculography because of incapacitating angina pectoris. These studies confirmed that patients with myxedema and severe angina tend to have severe proximal coronary artery disease, including left main coronary artery disease, and their conditions should be considered highly unstable. Four patients had saphenous vein bypass grafting to a mean of 2.8 vessels without complication. Preoperative thyroid hormone replacement ranged from 0 to 50 μg of L-thyroxine daily and postoperatively adequate thyroid hormone replacement was given to all patients without complications. Oral thyroid replacement begins to improve myocardial performance only when replacement therapy reaches an equivalent of 50 to 70 μg of thyroxine daily.

232 Hemodynamic Benefits of Atrioventricular Sequential Pacing After Cardiac Surgery

GEOFFREY O. HARTZLER, JAMES D. MALONEY, JACKIE J. CURTIS and DONALD A. BARNHORST

This study of the hemodynamic effects of atrioventricular (A-V) sequential pacing in 10 patients with and without heart block after cardiac surgery demonstrates the importance of atrial systole in the abnormal heart after surgery. Ventricular pacing alone proved hemodynamically detrimental or of no benefit in six of the eight patients who initially had sinus or accelerated junctional rhythms. Atrial pacing alone produced significant improvement in cardiac output in all patients who were not pacemaker-dependent. A-V sequential pacing using optimal A-V intervals produced maximal cardiac output. Significant changes in cardiac output occurred with relatively small deviations in the A-V interval. However, A-V sequential pacing cannot be performed reliably or profitably in patients with persistent atrial tachycardias, flutter or fibrillation or in those receiving infusions of sympathomimetic amines postoperatively.

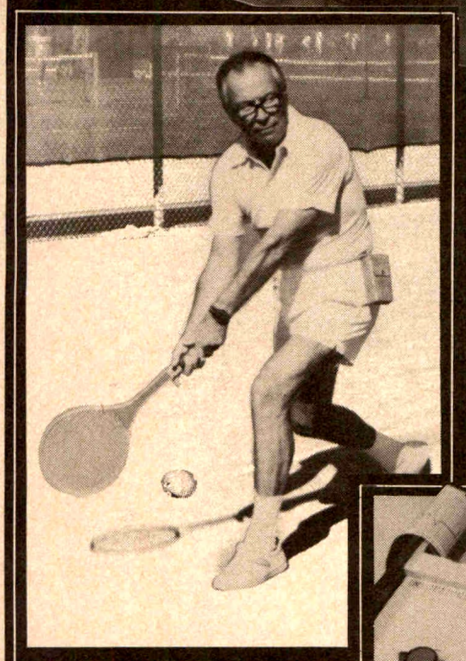
Continued on page A20



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METHODS

237 Clinical Use of A New Transvenous Atrial Lead

M. KLEINERT, M. BOCK and F. WILHEMI

Although atrial programmed cardiac stimulation offers the most physiologic form of treatment for the patient with bradyarrhythmia, the implantation rate for such pacemakers is only 1 percent worldwide, primarily because of past difficulties in securely positioning transvenous atrial electrodes for long-term pacing. This report of experience with a new J type atrial lead in 53 patients provides encouraging results. This lead, which continues to perform well in 52 patients, was easily and quickly implanted in the right atrial appendage within an average of 5 minutes after the selected vein was opened. It also demonstrated very positive technobiologic properties, including a relatively high atrial action potential averaging 5.17 mv, and a low 6 percent dislodgment rate.

REVIEWS

243 Exercise Testing in the Diagnosis of Coronary Heart Disease: A Perspective

LENORE R. ZOHMAN and ALBERT A. KATTUS

Examining the methods of assessing the diagnostic usefulness and limitations of exercise testing to detect coronary obstructive disease, these investigators note that the sensitivity level of an exercise test is low if the test is expected to detect 50 percent obstruction of a coronary vessel. There is greater concurrence of exercise test and angiographic findings if 75 percent rather than 50 percent obstruction is the goal for detection. For maximal diagnostic sensitivity exercise testing must be carried to physiologic or symptom-limited maximal effort. Diagnostic exercise testing patterns should allow patients enough time at each stage to achieve a steady state. Clinical interpretation of an exercise test is greatly enhanced by taking into consideration the electrical (electrocardiograph), hemodynamic (blood pressure) and symptomatic (angina) components of the ischemic response to exercise testing. Angina or progressively decreasing systolic blood pressure during increasing work load is a strong indicator of myocardial ischemia. Data in 205 consecutive exercise tests on patients in a large cardiology consulting service in whom the prevalent rate of coronary disease is high show that both the sensitivity and the specificity levels of the exercise test are also high.

251 Primary Prevention of Coronary Heart Disease: A Critique

NEMAT O. BORHANI

This thoughtful examination of the evidence concerning primary and secondary prevention of coronary heart disease concludes that the data justify only serious consideration of a strategy to prevent the smoking habit, persuading patients to stop and encouraging teenagers not to start. On the other hand, despite the emphasis on serum cholesterol-lowering measures, the available clinical trials indicate that such measures may indeed reduce cholesterol but do not significantly lower morbidity or mortality rates for coronary artery disease. Community clinical trials of hypertension control now underway in the United States are important in providing answers about the value of such detection and treatment of hypertension in preventing coronary heart disease and reducing its mortality and morbidity. Arterial blood pressure is a biologic quantity with a continuous distribution and all treatment plans should be individualized according to the needs of the patient.

Continued on page A22

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PROGRESS REPORT

260 Collaborative US-USSR Study on the Prevalence of Dyslipoproteinemias and Ischemic Heart Disease in American and Soviet Populations

Prepared by the US-USSR Steering Committee for Problem Area 1: the Pathogenesis of Atherosclerosis.

This ongoing collaborative US-USSR study of the prevalence of dyslipoproteinemias, based on the Lipid Research Clinics Study protocol, is designed to investigate the relation of plasma lipids and lipoproteins and other risk factors to atherosclerotic disease in selected populations. Preliminary comparative data for men aged 40 to 59 years show that total plasma cholesterol levels are higher in the Soviet than in the North American sample; plasma triglycerides are 25 mg/dl higher in the North American sample; and the high density lipoprotein cholesterol level is 8 to 10 mg/dl higher in the Soviet sample. This US-USSR Collaborative Study appears to provide an appropriate framework for communication among scientists of both countries.

HISTORICAL MILESTONES

269 Diagnosis of Myocardial Infarction: Historical Notes From the Soviet Union and the United States

JAMES E. MULLER

The Russian physicians V. P. Obraztsov and N. D. Strazhesko published the first complete clinical description of myocardial infarction in 1910. Two years later James B. Herrick, citing a German translation of the Russian article, described this disease for American physicians, stimulated the development of the electrocardiogram for its diagnosis and correctly anticipated the current interest in limitation of infarct size.

DIAGNOSTIC SHELF

272 Echocardiographic Features of Right Ventricular Outflow Tumor Prolapsing Into the Pulmonary Artery

NAVIN C. NANDA, S. SERGE BAROLD, RAYMOND GRAMIAK, LING S. ONG and ROBERT A. HEINLE

M mode echocardiographic studies of the pulmonary valve were performed in a 19 year old woman presenting clinically with bacterial endocarditis involving a mildly stenotic valve. They proved essential in determining the site of attachment and mobility characteristics of a large myxoma of the right ventricular outflow tract with a polypoid extension that projected into the pulmonary artery in systole and contained a fibrous vegetation at its top. A two dimensional echocardiogram clearly showed a portion of the mass passing beyond the position of the pulmonary valve into the main pulmonary artery and returning into the right ventricular outflow tract during diastole. The tumor, together with its stalk and a small portion of the right ventricular wall, was successfully resected.

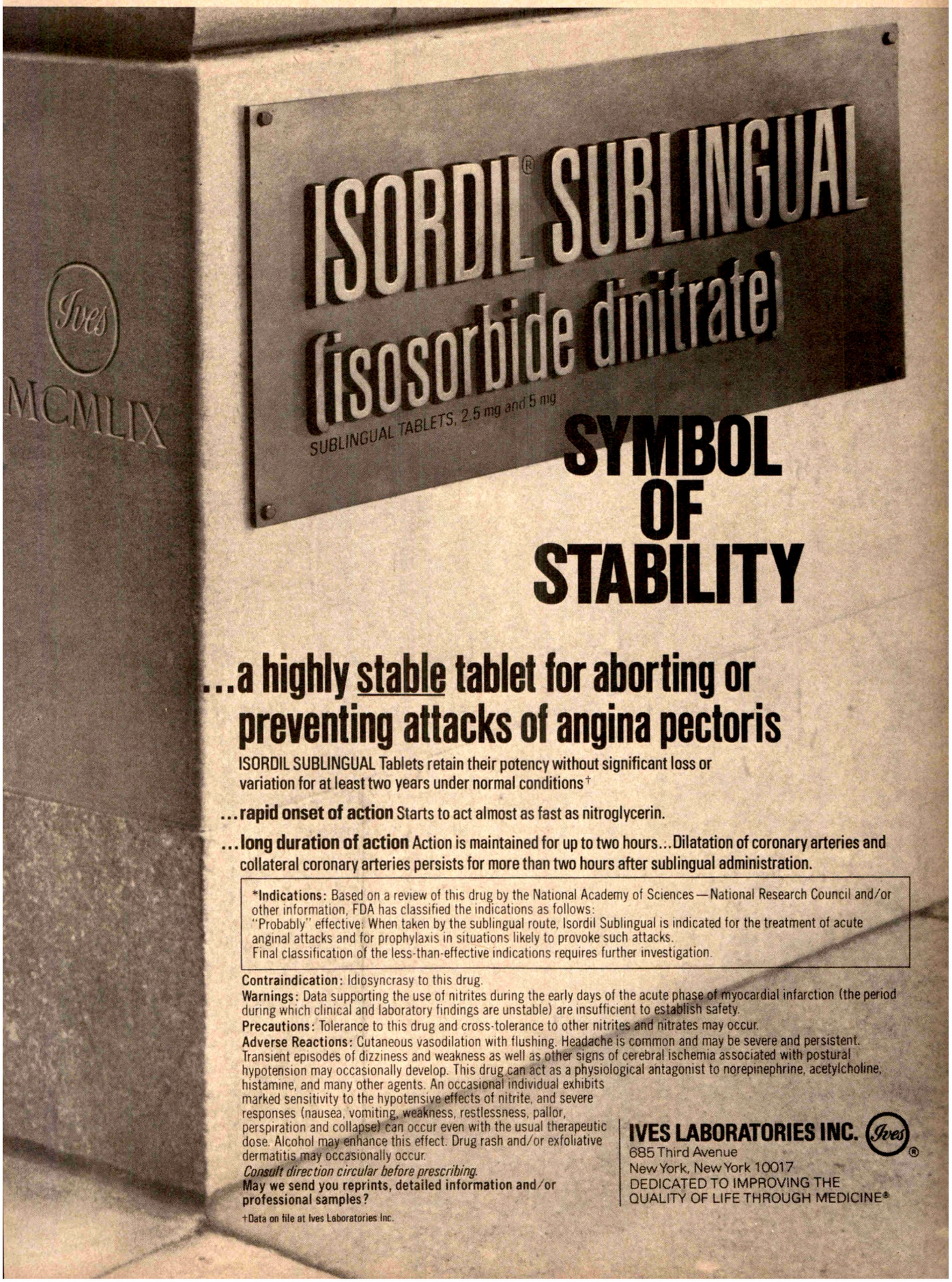
277 Thallium-201 Imaging With Color Display Computer System in Old Myocardial Infarction

TOSHITAMI SAWAYAMA, YASUHIKO ITO, TSUNEJI ICHIKAWA, SHOSO NEZUO, TSUKASA TSUDA and TATSUKI KATSUMURA

These results in 13 patients with old myocardial infarction and in 11 patients without infarction suggest that the use of a color display computer system greatly enhances the sensitivity of thallium-201 imaging and the objective and qualitative analysis in diagnosing old myocardial infarction. The nine colors used in this system allow more exact definition of regions of reduced isotope uptake, and the computer system allows more quantitative evaluation of uptake in regions of interest.

Continued on page A24

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Probably" effective: When taken by the sublingual route, Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

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CASE REPORTS

282 Cardiac Death in Mucocutaneous Lymph Node Syndrome

STANLEY M. KEGEL, THOMAS J. DORSEY, MARSHALL ROWEN and WILLIAM F. TAYLOR

This paper describes a 12 year old Nisei boy in the United States who first showed symptoms of coronary artery disease 4 years after recovery from the mucocutaneous lymph node syndrome and died suddenly from extensive myocardial infarction while awaiting scheduled coronary arterial surgery. Such sudden cardiac deaths are not unusual, occurring in about 2 percent of reported cases as a result of myocardial infarction or cardiac arrhythmia, usually during the third or fourth week of the illness. Postmortem examination in fatal cases has uniformly revealed coronary arterial aneurysms with occlusion due to thromboendarteritis. All children with this syndrome should have extensive cardiac evaluation during the acute illness. Coronary arteriography is indicated in those with evidence of significant cardiac involvement.

287 Isolated Coronary Periarteritis: Report of a Case of Unexpected Death in a Young Pregnant Woman

JACQUES H. AHRONHEIM

The isolated coronary periarteritis and acute thrombosis causing sudden, unexpected death of a 23 year old woman in her 8th month of pregnancy were found at autopsy to be secondary to an inflammatory infiltrate in the adventitia. A hypersensitivity factor is the most likely cause of the infiltrate. This case suggests a relation, not yet clearly definable, between pregnancy and such fatal inflammatory coronary artery disease.

EDITORIALS

291 Appraisal of Treatment for Left Main Coronary Artery Disease

ABDULMASSIH S. ISKANDRIAN, BERNARD SEGAL and ELDRED D. MUNDTH

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Mid Ventricular Obstructive Cardiomyopathy Versus Ventricular Aneurysm—S. M. Alipour, G. Rao and R. E. Falicov

Echocardiogram in Aortic Stenosis—R. Bassan, W. E. Hellenbrand and N. S. Talner

Cardiac Arrhythmias After Psychotropic Drugs—A. J. Gelenberg and N. O. Fowler, et al.

Vectorcardiographic Criteria for Diaphragmatic Myocardial Infarction—M. L. Fisher, M. Mugmon and P. D. Stein, et al.

299 Books Received

301 American College of Cardiology News

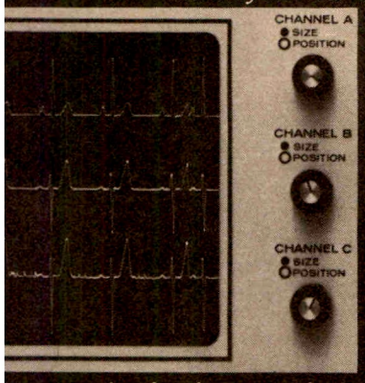
CORRECTION

The name of Dr. Menashe Waxman, third author of the article by Geer et al. on "Chronotropic Effect of Acetylstrophanthidin Infusion Into the Canine Sinus Nodal Artery," on pages 684 to 689 of the May 4, 1977 issue of the Journal, was incorrectly spelled Wasman in the Table of Contents of that issue and again in the Author Index in the June issue. We regret the error.

HOW DOES QUINTON'S 3-CHANNEL MONITOR IMPROVE YOUR EXERCISE TESTING EFFICIENCY?

Designed for the real world. Take one look at our new three channel exercise testing monitor and you can see that it's designed as a practical working tool.

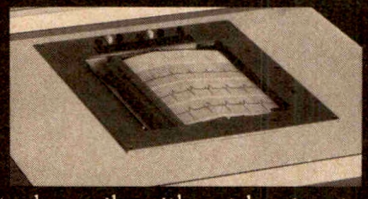
The entire system is built into one sturdy, compact unit.



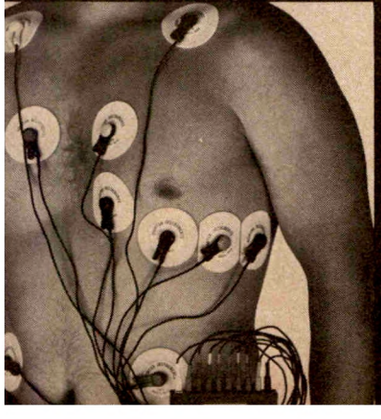
Three channel, no fade scope. The Model 633 displays three channels on the scope and records three channels on the recorder. With the "write-from-memory" feature, you can freeze a particular scope image, study it and record it for future reference.

Automatic lead rotation. Quinton's auto lead rotation changes lead groups automatically, making it easy to do full 12 lead resting ECG's before and after the exercise test.

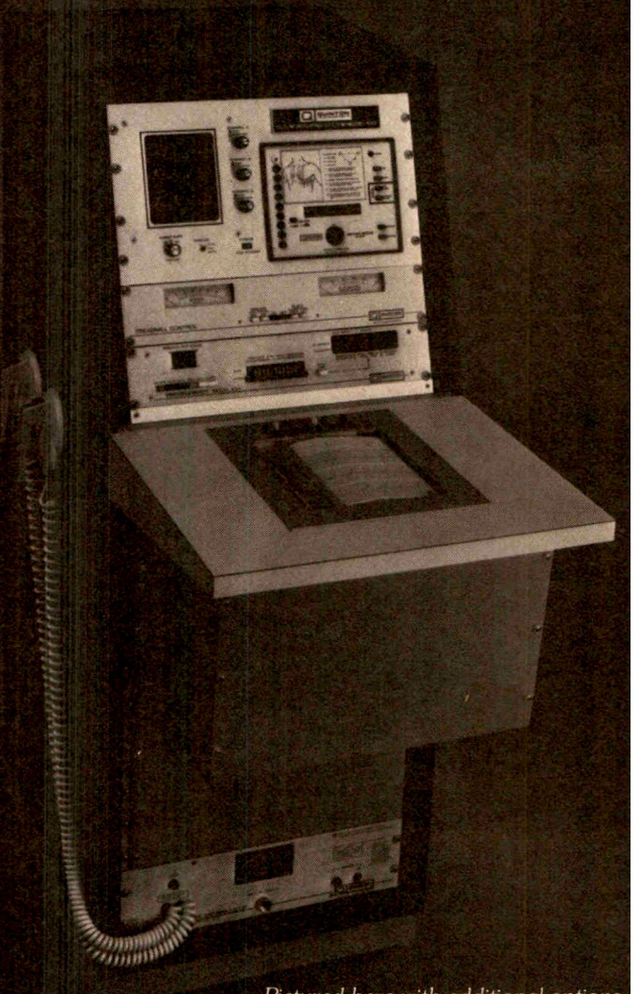
Easy to use. The recorder is mounted in a convenient desk top working area just below the control panel. You can make notes and adjust controls easily without having to reach or move around the unit. A handy storage area is located beneath the recorder desk.



Signal processing output. In addition to the full three channels displayed, every model 633 comes with a fourth channel output which can be connected to a signal processor or computer for signal averaging or S-T Segment analysis.



Low noise, shielded cable. Each Model 633 comes equipped with a special low noise, shielded patient cable to minimize extraneous noise and motion artifact. No battery pack is required.



Pictured here with additional options.

Tailored to your needs. Before your Model 633 leaves the factory, you can have it set to automatically monitor the specific exercise lead group you select.

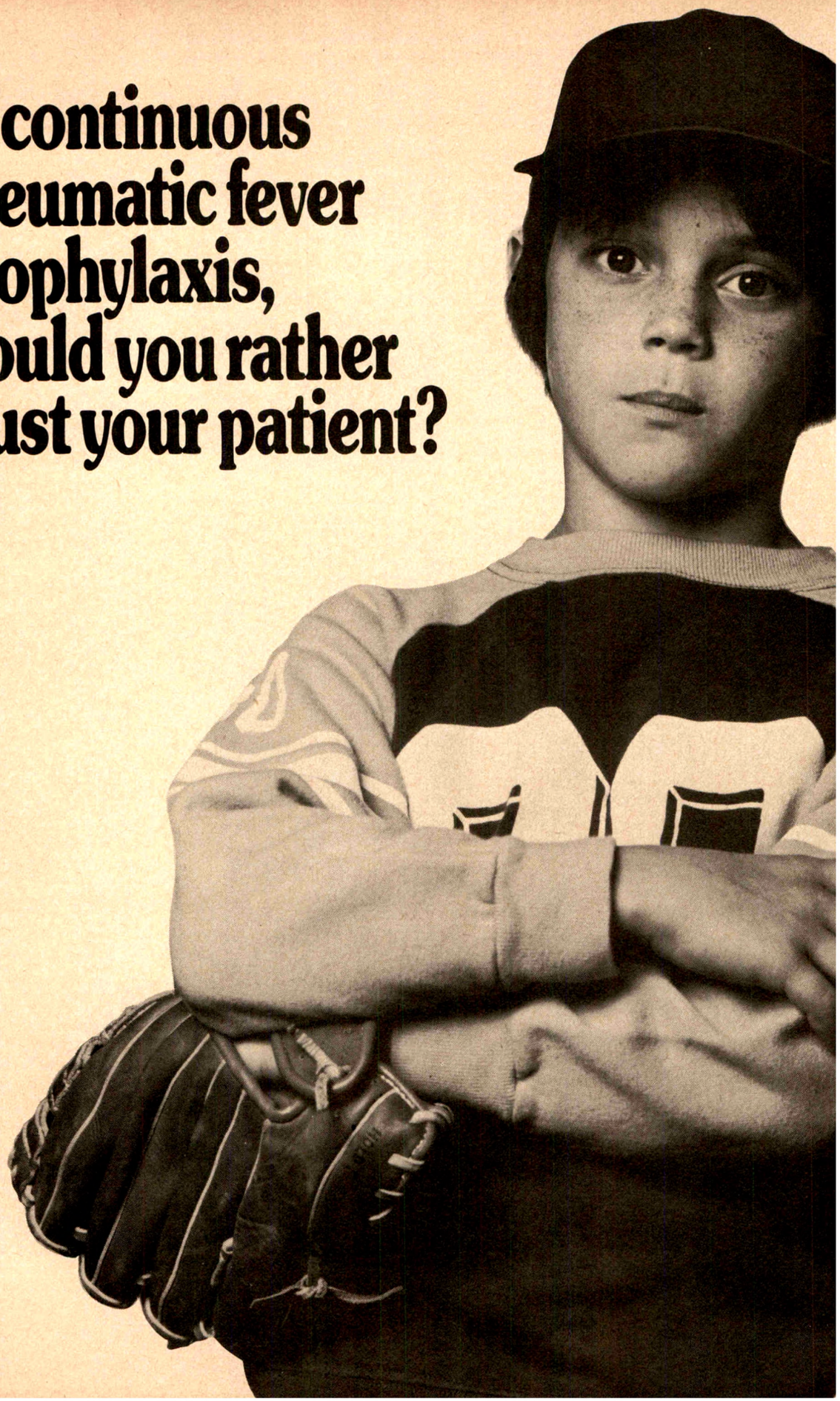
For more information, contact Quinton Instrument Co., Dept. E106, 2121 Terry Avenue Seattle, Washington 98121. Call Toll Free 800-426-0538.



IN THE LONG RUN- DEPEND ON QUINTON

QUINTON

In continuous rheumatic fever prophylaxis, would you rather trust your patient?



Or yourself?

Injection penicillin G benzathine is recommended as the method of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever. One reason is that just one injection of 1,200,000 units, once a month, usually offers effective and continuous prophylaxis. So there's no need to worry that your patient will forget to take a tablet every day.

Mild to moderate group A streptococcal pharyngitis (without bacteremia) therapy is in your hands, too. Because a single injection (600,000 to 900,000 units in children and 1,200,000 units in adults) usually maintains serum concentrations for the ten days deemed necessary to eradicate the streptococci and preclude the initial onset of rheumatic fever.†

You, more than anyone else, know the importance of effective and continued rheumatic fever prophylaxis. So is there any question of whom you'd rather trust?

*Rheumatic Fever Committee of the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association.

FOR DEEP INTRAMUSCULAR INJECTION ONLY.
Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A — without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections — Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea — Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

†In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units penicillin G benzathine as active ingredient in aqueous suspension): 300,000 units per ml. — 10-ml. multi-dose vial. Each ml. also contains sodium citrate buffer, approximately 6 mg. lecithin, 3 mg. povidone, 1 mg. carboxymethylcellulose, 0.5 mg. sorbitan monopalmitate, 0.5 mg. polyoxyethylene sorbitan monopalmitate, 1.2 mg. methylparaben and 0.14 mg. propylparaben.

600,000 units in 1-ml. TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-ml. fill in 2-ml. TUBEX, packages of 10.

1,200,000 units in 2-ml. TUBEX, packages of 10, and in 2-ml. single-dose disposable syringe, package of 10.

2,400,000 units in 4-ml. single-dose disposable syringe, packages of 10.

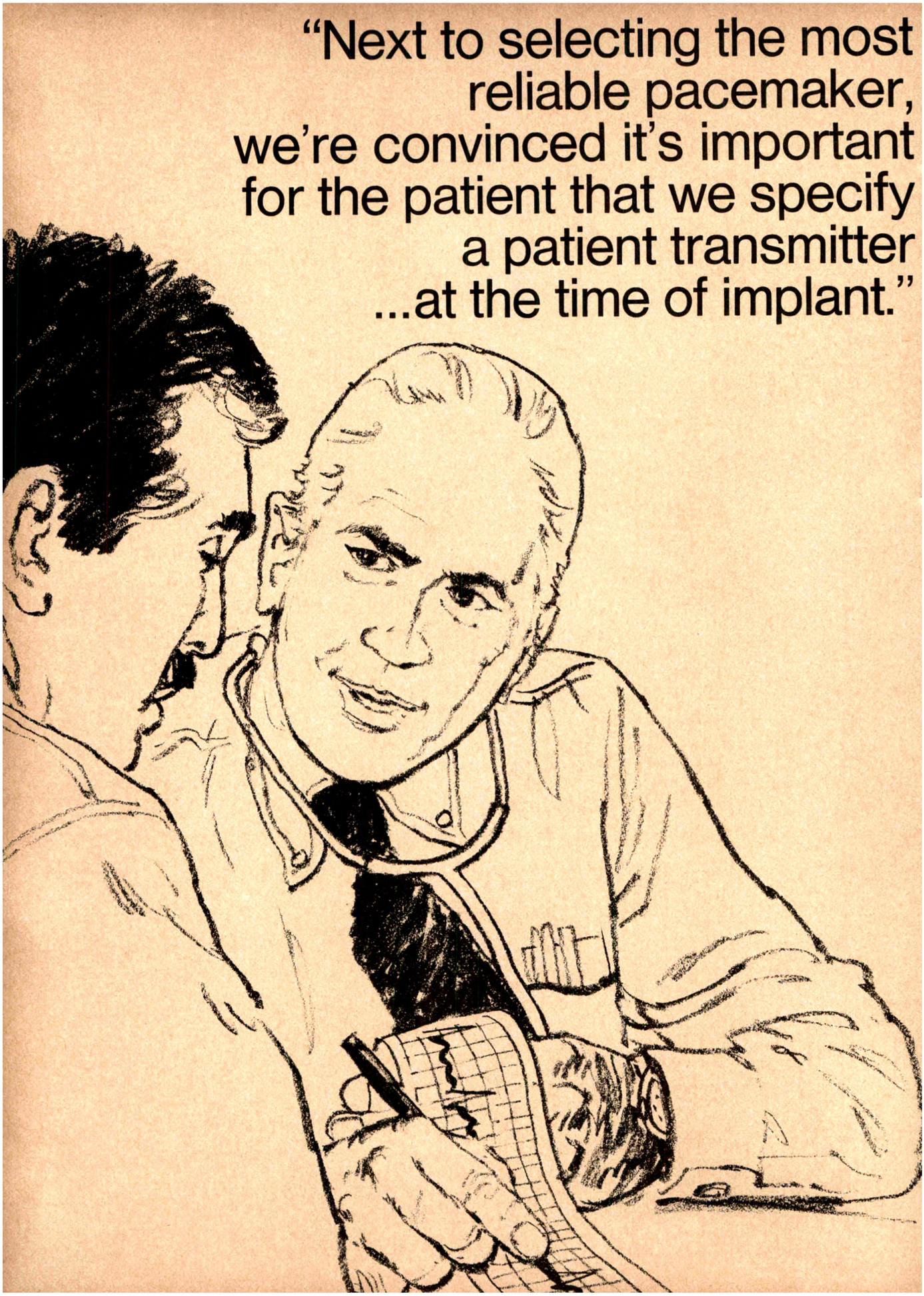
Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.

INJECTION
Bicillin® L-A
(sterile penicillin G benzathine suspension)

Once-a-month rheumatic fever prophylaxis.

Wyeth Laboratories
Philadelphia, Pa. 19101

"Next to selecting the most reliable pacemaker, we're convinced it's important for the patient that we specify a patient transmitter ...at the time of implant."



The ESB Medcor Pacer System. It's a pacer and a patient transmitter which provide the ultimate in pacer therapy . . . through the convenience of complete pacer—and patient—check-up by telephone from the time of implant. It's the *only* system that combines components designed, engineered and precision-made by the same manufacturer for total patient management: a clinically proven lithium pacer interfacing with the monitoring transmitter used by more pacer patients than any other.

The LITHICRON Model 3-70C lithium pacemaker. Ultra thin (1.40 cm) and lightweight (73 grams), the Lithicron has a calculated life expectancy of up to 10 years. Lithium power cells with the highest energy density of any pacemaker, *plus* the proven integrity of the ESB Medcor electronic circuitry make the difference. Both the Lithicron cell system and the Lithicron circuitry are hermetically sealed in a case of lightweight titanium . . . for maximum protection against invasion of body fluids, and resistance to electromagnetic interference.



The PACER-CHECK® system transmitter. No other transtelephonic monitoring unit provides more useful data for post-implant pacing surveillance. The lightweight, portable Pacer-Check patient unit transmits pacer rate and/or interval, patient ECG with pacer artifact for sensing/capture evaluation—even pulse-width measurement—direct to the receiving unit by telephone between two points anywhere in the world. Just a 2-minute call gives you the data you need for complete patient follow-up at any time. And gives your patient a sense of confidence and security not otherwise possible.

The cost of the ESB Medcor Pacer System? It can be substantially less than the combined cost of the individual components, resulting in both clinical and administrative cost effectiveness.

Now, pacing state-of-the-art technology makes it especially beneficial for you—and your patients—to specify a pacemaker system when you specify the pacer. Our representative can help you implement the *one* system made to work together—The ESB Medcor Pacer System. For the name of the representative in your area, or for more information, write: ESB Medcor, Inc., Dept. B., 5920 Rodman Street, Hollywood, FL 33023. Or call toll-free 800-327-9780.

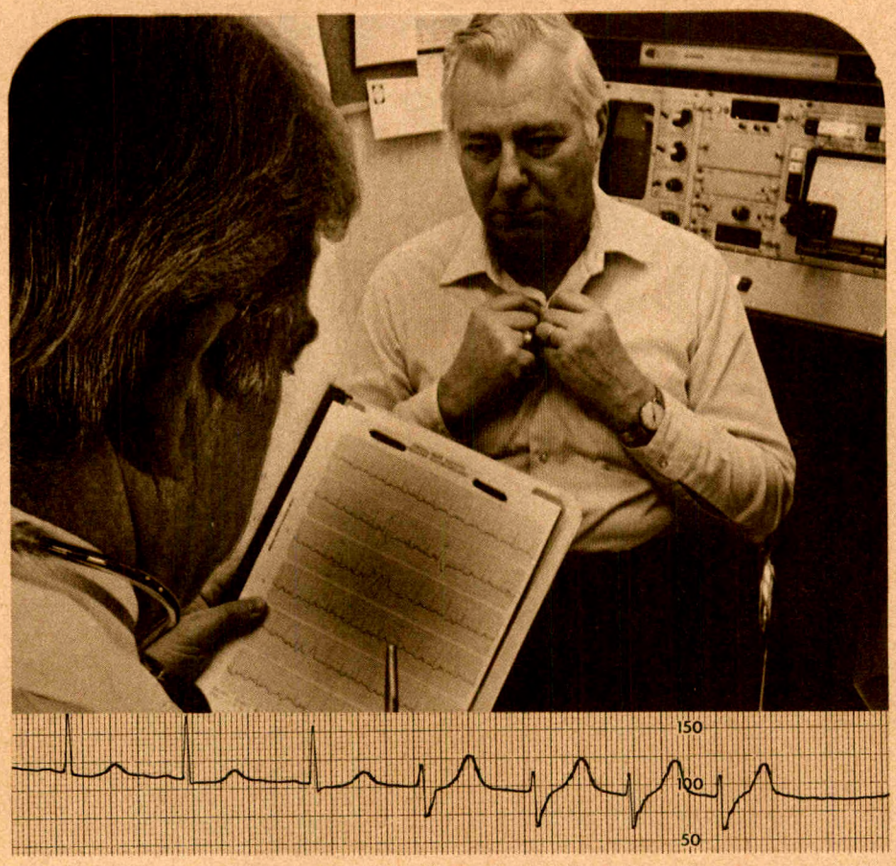
ESB Medcor™

ESB MEDCOR, INC.
5920 Rodman Street
Hollywood, Fla. 33023

*In Florida call collect 305-966-5900.

diagnosis: PVCs

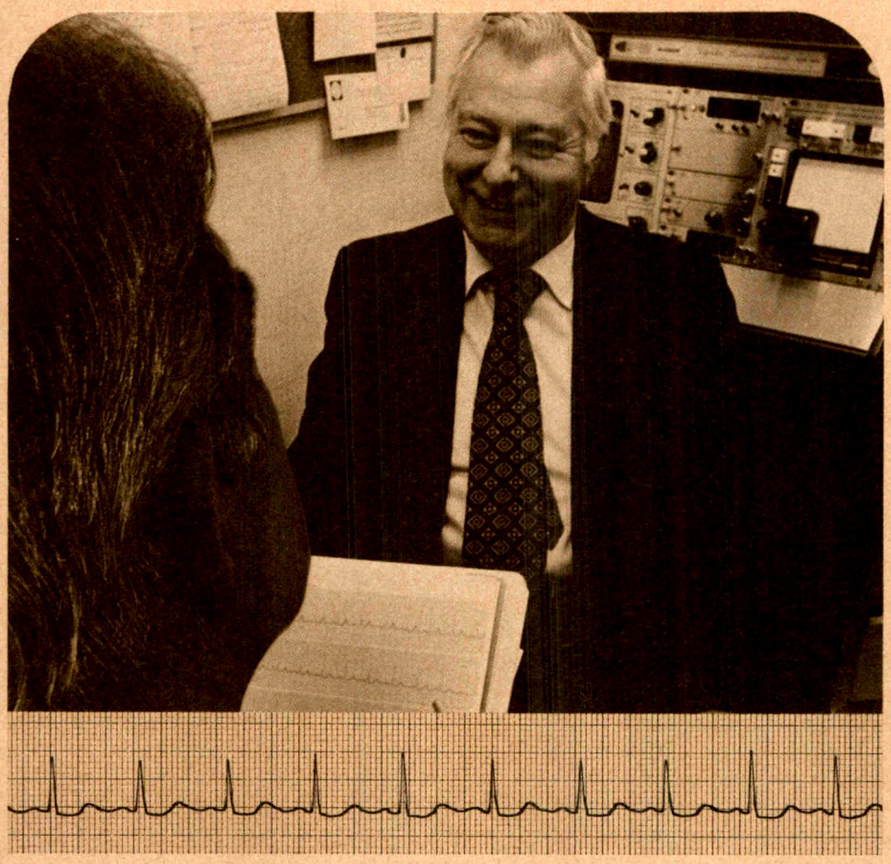
(Premature Ventricular Contractions)



initial therapy: quinidine sulfate tablets at

9 a.m.
1 p.m.
5 p.m.
9 p.m.

Then, for convenience and compliance...



a welcome change-simple q 8-12 hour dosage

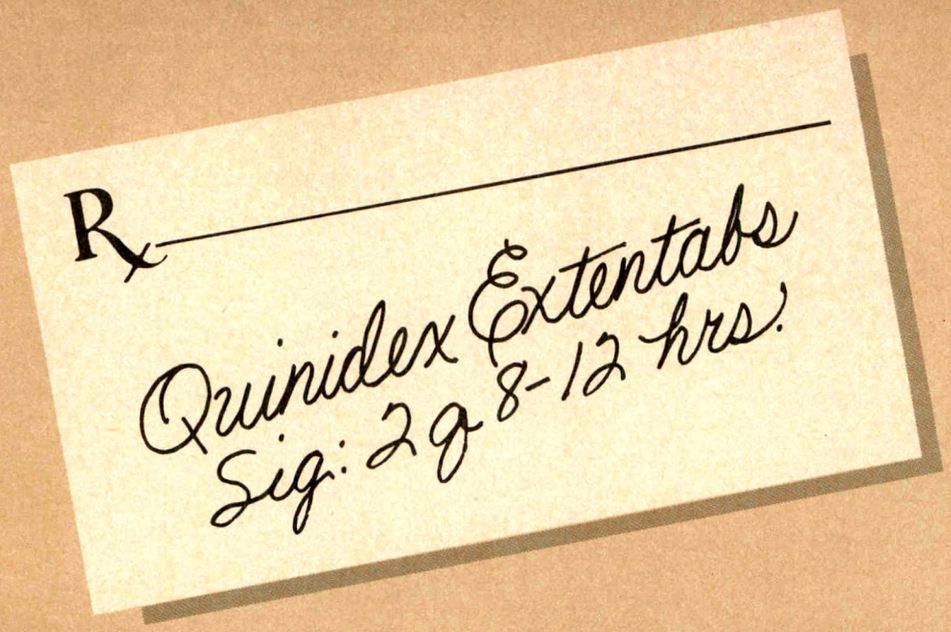
Quinidex Extentabs®

(Quinidine Sulfate, USP)

After the PVC's have been successfully suppressed with quinidine sulfate tablets, you can *maintain* normal sinus rhythm with Quinidex Extentabs. The simple q 8-12 hour dosage is more convenient for the patient than the usual q.i.d. dosage for short-acting tablets. Instead of having to remember to carry his medication with him during the day, he simply leaves the bottle in the medicine cabinet. There's less risk of a missed dose . . . better compliance with your dosage regimen. The unique construction of Quinidex Extentabs provides continuous absorption of quinidine sulfate over an 8-12 hour period. Each of the Extentabs contains 300 mg quinidine sulfate-approximately 23% more quinidine alkaloid than 325 mg quinidine gluconate.

A·H·ROBINS

See full prescribing information on following page.



Indications:

Quinidex Extentabs are indicated in the treatment of:

Premature atrial and ventricular contractions.
Paroxysmal atrial tachycardia.
Paroxysmal A-V junctional rhythm.
Atrial flutter.
Paroxysmal atrial fibrillation.
Established atrial fibrillation when therapy is appropriate.
Paroxysmal ventricular tachycardia when not associated with complete heartblock.
Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

The only long-acting form of quinidine sulfate

Quinidex® Extentabs

(Quinidine Sulfate, USP)

ROBINS

A·H·ROBINS

A. H. Robins Company, Richmond, Va. 23220

Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

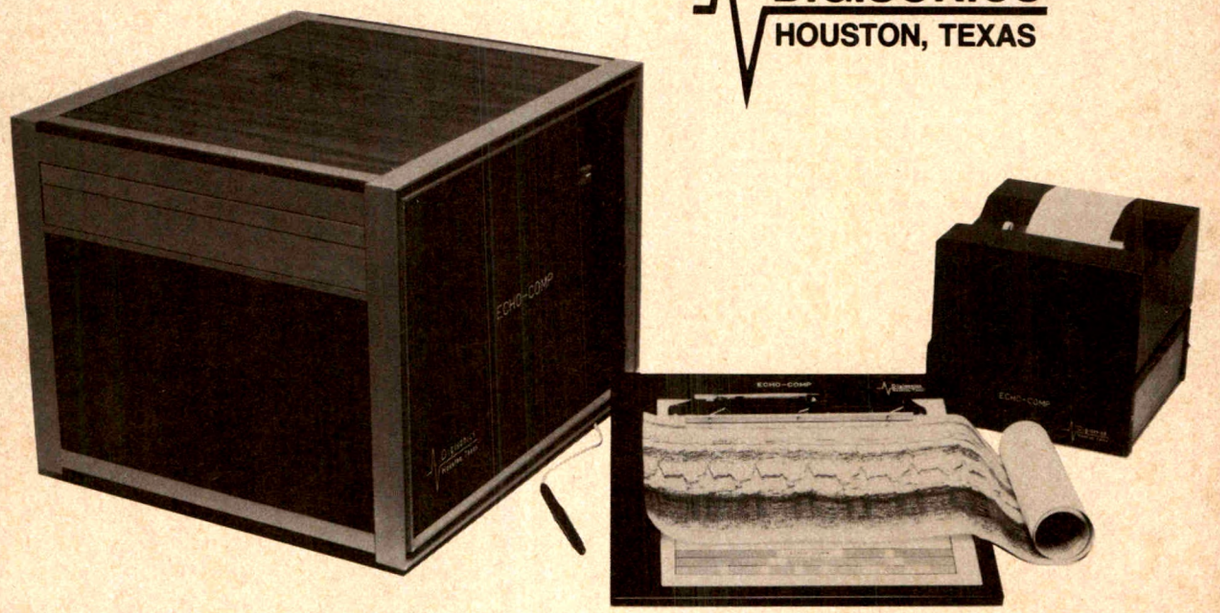
Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 and 250 (NDC 0031-6649).

ECHO-COMP

The M-mode Calculator from

DIGISONICS
HOUSTON, TEXAS



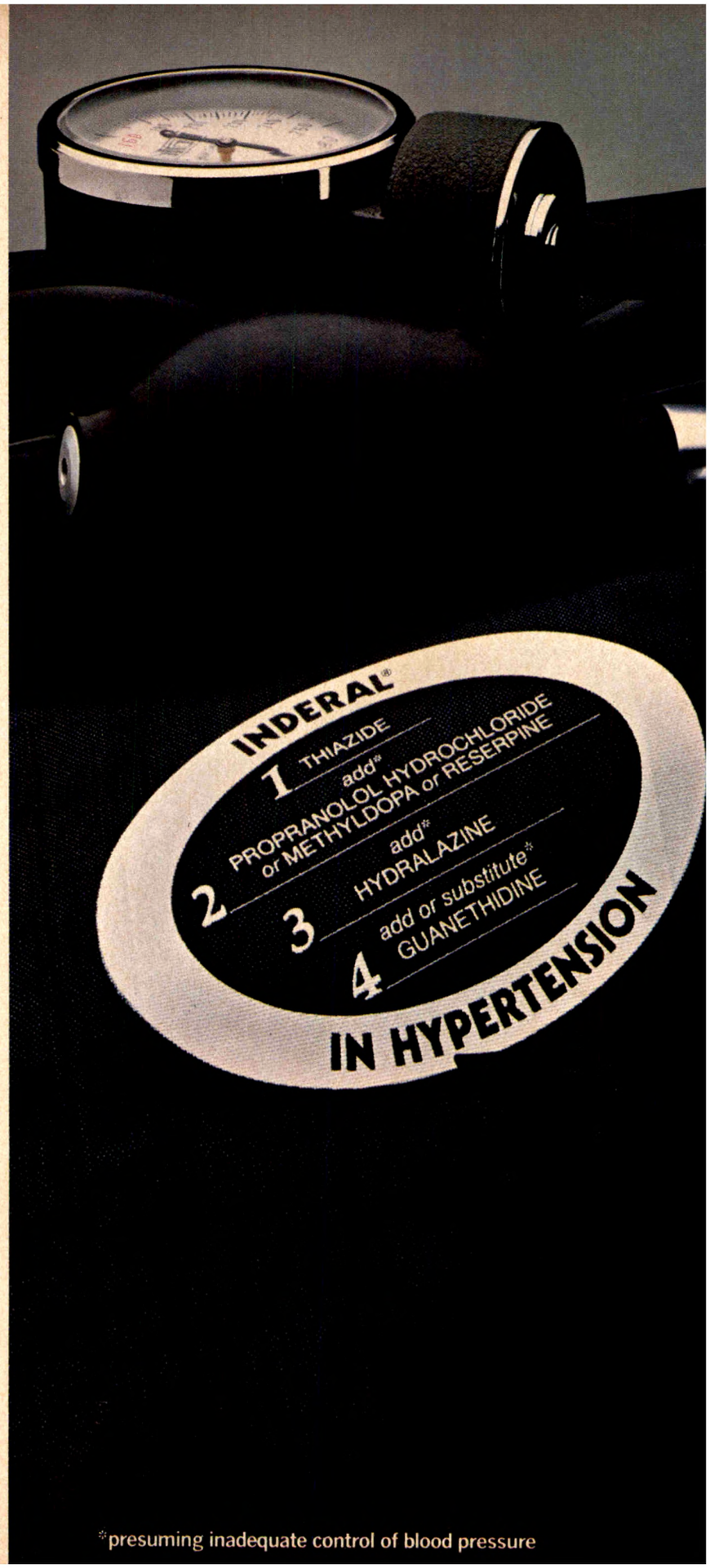
ECHO-COMP provides automatic calculation of over 70 typical M-mode measurements including excursions, times, velocities, dimensions, ratios, body surface area corrections, heart rate corrections, and statistics. The Area/Volume option is used to calculate areas, volumes and related parameters from two dimensional images.

ECHO-COMP consists of a programmed mini-computer, a digitizer, and printer. The operator specifies calculations to be done by touching the appropriate buttons on the control console. Data points are entered by touching them with a special pen. Results are immediately printed. Subsequent statistical analysis or body surface area corrections can also be done.

DIGISONICS
3701 KIRBY DRIVE
HOUSTON, TEXAS 77098
CALL TOLL-FREE (800) 231-3490

INDERAL®
(propranolol hydrochloride)

Official recognition of clinical success: the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure has revised its recommendations for the stepped-care treatment of hypertension and officially designated INDERAL as one of the choices for use in Step Two, should blood pressure control with a thiazide diuretic prove inadequate.[1]



Ayerst®

*presuming inadequate control of blood pressure

INDERAL®
(propranolol hydrochloride)
IN HYPERTENSION

A PATTERN OF CLINICAL SUCCESS

In study after study... INDERAL continues to prove highly effective in helping to control mild to severe hypertension.

INDERAL has been used to establish control in inadequately controlled hypertension. INDERAL, added to or substituted in the regimen, effectively lowers blood pressure in many cases where diuretics, reserpine, methyldopa, or hydralazine are unable to provide sufficient antihypertensive effect.[2-12] Moreover, INDERAL is equally effective in both the supine and standing positions.[2,5-9] It, therefore, tends to provide smooth 24-hour control of blood pressure.

Tolerance to INDERAL has not been observed.[13]*

INDERAL is a drug of choice for use with diuretics to provide greater blood pressure control,[1] and to which hydralazine is added when needed.

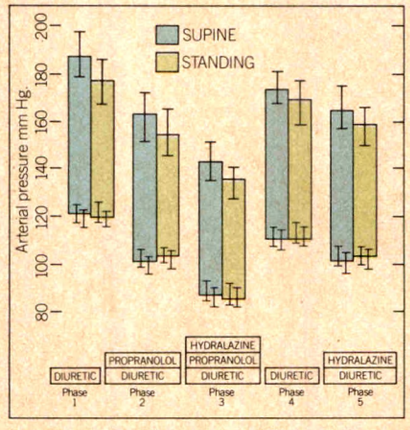
When combined with these agents, INDERAL has an additive antihypertensive effect. Furthermore, INDERAL offsets reflex increases in cardiac rate, cardiac output, and renin secretion which tend to diminish the efficacy of diuretics[14,15] and vasodilators.[7,8,14,16-19] INDERAL thus is a rational addition to therapy when the antihypertensive capacity of a diuretic alone proves insufficient.

By inhibiting reflex increases in heart rate and cardiac output, INDERAL also extends the usefulness



of hydralazine. When hydralazine is added to INDERAL, the dose of both drugs can often be reduced.

The combination of INDERAL plus hydralazine has aptly been called "hemodynamically unique" and when added to a diuretic provides an effective regimen for most moderate to severe hypertensive patients.[17]



Before entry into the five-phase study, the blood pressures of 20 of the 23 patients were inadequately controlled by a diuretic plus either methyldopa, or guanethidine, or both. After establishment of blood pressure control with a diuretic plus INDERAL plus hydralazine, withdrawal of INDERAL reduced the antihypertensive efficacy of the resulting regimen by 50% and produced unacceptable side effects in 25% of the patients.

Adapted from Zacest, *et al.*[8]

INDERAL is associated with greater freedom from certain side effects which may impair the life-styles of active patients and may prevent compliance.

Because INDERAL blocks only beta-adrenergic activity, it does not tend to cause side effects characteristic of other potent antihypertensive agents which inhibit the entire sympathetic nervous system.[7,14,17]

Postural or exercise hypotension is not a problem with INDERAL.

Because it usually does not cause postural or exercise hypotension, INDERAL has been considered a drug of choice for those whose occupations, activities, or underlying conditions, such as cerebrovascular disease, would make a sudden fall in blood pressure dangerous.[2,5-9,13,16,20-23]

Sexual dysfunction is rarely, if ever, a problem with INDERAL.

Failure of erection or ejaculation does not characterize therapy with INDERAL.[6,7,15,20,22,23]*

Patient compliance can be enhanced.

The fact that INDERAL is generally well tolerated can be expected to have a favorable effect on patient compliance.[2,7,8]

In one recent study comparing the combination of a diuretic plus beta-blockers, including INDERAL, to previous therapy with a diuretic plus reserpine, or methyldopa, or other agents, patient preference for the beta-blocker regimen was so great that "no patient wished to return to former medication after the trial concluded, and many rated their general tolerance of treatment as considerably improved."[6]

*See subsequent discussion of untoward effects and full prescribing information for Contraindications, Warnings, Precautions, and Adverse Reactions.

INDERAL®
(propranolol hydrochloride)
IN HYPERTENSION

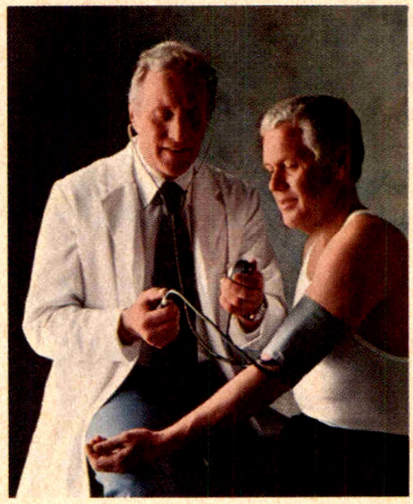
A PRESCRIPTION FOR CLINICAL SUCCESS

Candidates for INDERAL therapy: the majority of hypertensives...except those with impaired cardiac function or those prone to bronchospasm.*

One of the likely mechanisms whereby INDERAL lowers blood pressure is reduction in cardiac output. In patients without significant cardiac dysfunction, this is a logical, safe, and effective way to lower blood pressure. The large majority of hypertensive patients without previous episodes of congestive failure or extensive scarring from multiple myocardial infarctions are likely to do well on INDERAL therapy.

Because full sympathetic drive may be necessary to maintain adequate pumping action in patients with impaired cardiac function, INDERAL is contraindicated in those with congestive failure, unless the failure is secondary to a tachyarrhythmia treatable with INDERAL. INDERAL is also contraindicated in patients with bronchial asthma.

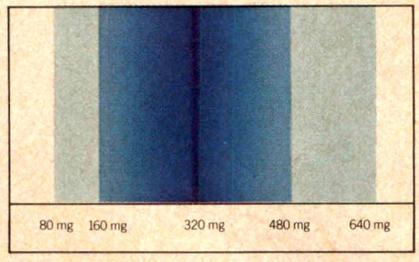
*See full prescribing information for Contraindications, Warnings, and Precautions on last page of advertisement.



Individualized dose titration: the key to better clinical results.

The recommended initial dose of INDERAL is 80 mg/day given in divided doses. The dose should be increased gradually until an optimum effect is achieved, usually in the range of 160-480 mg/day. In some instances, up to 640 mg/day may be required. Since a few days to weeks may be required for INDERAL to exert its full antihypertensive effect, sufficient time should be allowed for blood pressure response during the course of dosage adjustment.

INDERAL is customarily given in divided doses.



Usual INDERAL starting dose in hypertension: 80 mg/day.
Usually effective dose range: 160-480 mg/day.

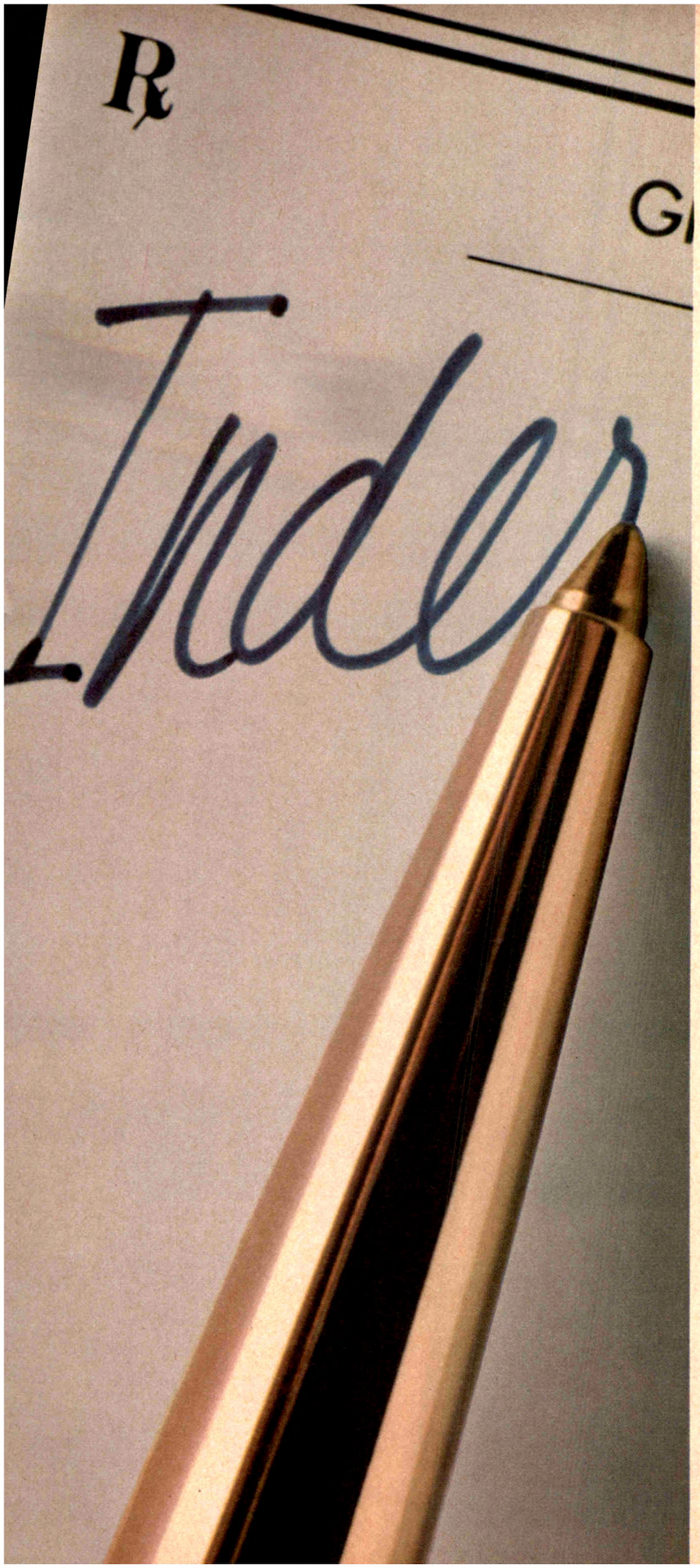
Lowering cardiac output is part of a rational approach to lowering blood pressure.

A slowing of heart rate and reduction of contractile force are among the probable mechanisms whereby INDERAL lowers blood pressure. As such, they should not be considered untoward effects.

Experience with INDERAL has shown that, "Since healthy individuals can sustain heart rates of 50 or less without any disability, there appears to be no reason for concern when propranolol induces heart rates of this level so long as there is no evidence of heart failure."[24]

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INDERAL®

Untoward cardiac effects are relatively infrequent.[13,15,16,23,24]

Congestive failure: Sympathetic inhibition with beta-blockade carries the potential risk of depressing myocardial contractility and precipitating cardiac failure in patients with, and, in rare instances, without a history of cardiac failure.

At the first sign or symptom of impending cardiac failure, the patient should be appropriately treated with digitalis and/or diuretics and the response closely observed. If cardiac failure develops, INDERAL should be withdrawn gradually unless immediate discontinuation is required by overriding clinical considerations.

INDERAL is also contraindicated in patients with a history of asthma.

Avoid abrupt withdrawal in patients with angina pectoris.

There have been reports of exacerbation of angina and, in some cases, myocardial infarction following abrupt discontinuance of INDERAL. INDERAL should be withdrawn gradually from patients with angina, and from any patients with possible inapparent atherosclerotic coronary artery disease.

All patients should be cautioned against interruption or cessation of therapy without the physician's advice.

Before prescribing INDERAL for hypertension, please consult prescribing information including additional Contraindications, Warnings, and Precautions on the following page.

Ayerst®

(For full prescribing information, see package circular.)

INDERAL®
Brand of propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

INDICATIONS

Hypertension

INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

Pheochromocytoma

After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase



DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is *different* for each indication.

ORAL

HYPERTENSION—*Dosage must be individualized.*

The initial dose is 80 mg INDERAL daily in divided doses. The dose may be increased gradually until optimum blood pressure response is achieved. The usual effective dose range is 160 to 480 mg per day. In some instances dosages of 640 mg per day may be required. The time course of full blood pressure response is variable and may range from a few days to several weeks. INDERAL is usually used in conjunction with other antihypertensive agents, particularly a thiazide diuretic. When INDERAL is employed as the sole therapeutic agent, concomitant dietary sodium restriction may be advantageous.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.

—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL (propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

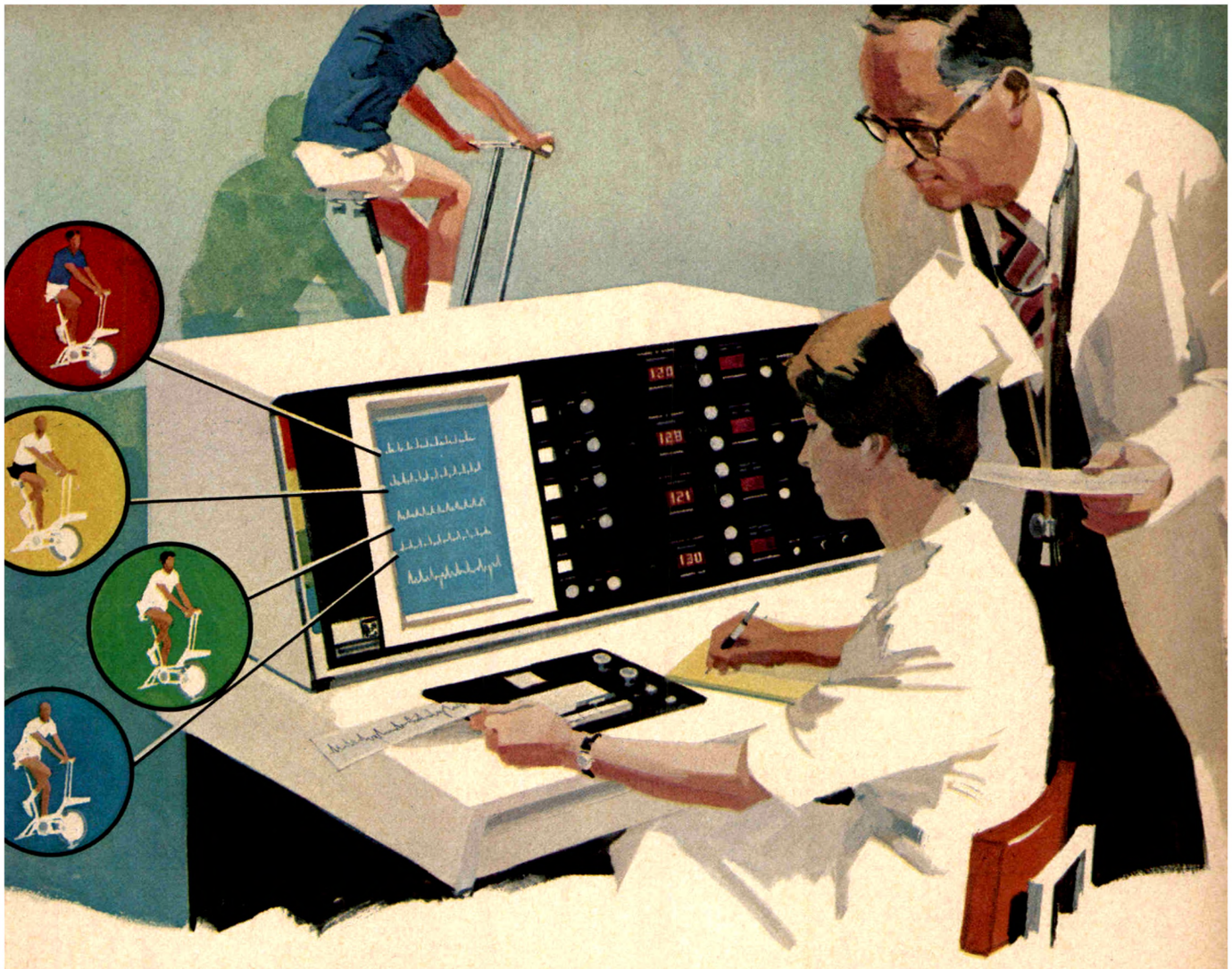
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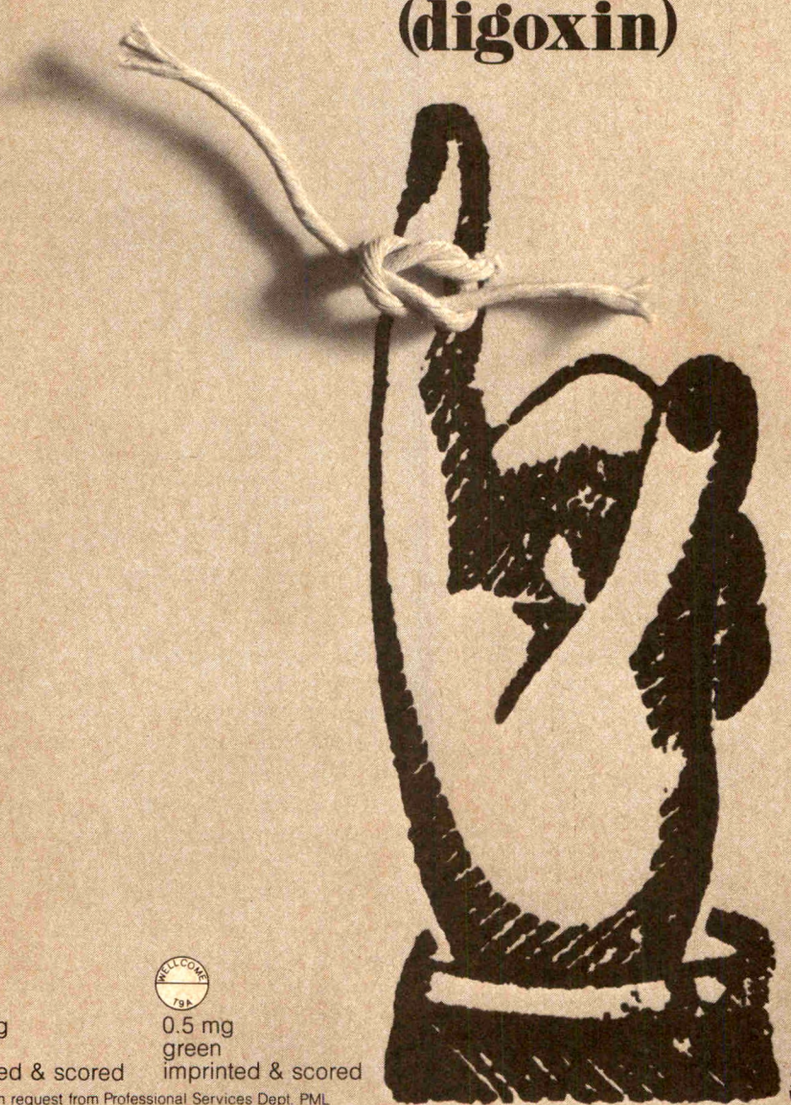
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CLINICAL STUDIES

Dual Myocardial Imaging With Technetium-99m Pyrophosphate and Thallium-201 for Detecting, Localizing and Sizing Acute Myocardial Infarction

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In order to assess and compare the sensitivity and accuracy of technetium (Tc)-99m pyrophosphate and thallium-201 (Tl-201) in detecting, locating and sizing acute myocardial infarction with respect to the biochemically measured extent of infarction, myocardial imaging with both agents using a gamma scintillation camera was performed in 35 patients with documented acute myocardial infarction within 1 to 5 days after the onset of acute symptoms. Tc-99m pyrophosphate scintigrams were abnormal in 30 patients (86 percent) and the location of uptake corresponded to the electrocardiographic site of the infarct in 23 of the 30 patients (77 percent). The five negative Tc-99m pyrophosphate scintigrams included two from patients with a subendocardial infarction. By contrast, all 35 Tl-201 myocardial images showed areas of decreased uptake and 33 (94 percent) corresponded to the electrocardiographic location of the infarct. In three patients with a prior myocardial infarction, separate defects were noted in addition to areas of decreased Tl-201 uptake corresponding to new Q waves and ST-T wave changes. Additional abnormal areas in the scintigrams not suggested by the electrocardiogram were noted with Tc-99m pyrophosphate in 9 patients and with Tl-201 in 16 patients; in 6 of these patients these areas were identical in extent and location in both radionuclide studies. In patients with negative Tc-99m pyrophosphate scintigrams, the average infarct size obtained from completed creatine kinase (CK) curves using serial serum CK values was smaller at 3.2 ± 0.5 (standard error) IU/liter·hour than in those with positive images (26.9 ± 4.1 IU/liter·hour; $P < 0.02$). The planimetered area of Tc-99m pyrophosphate uptake that projected largest in one of the three views averaged 33.2 ± 4.6 cm^2 in patients with anterior or lateral infarction but only 18.9 ± 2.5 cm^2 ($P < 0.03$) in patients with inferior infarction, whereas mean infarct size as assessed with CK values was not different in both groups. Correlation between infarct size as assessed with CK curve and area as assessed with Tc-99m pyrophosphate uptake was good ($r = 0.90$) in anterior infarctions but only fair ($r = 0.64$) in inferior infarctions.

The data indicate that Tl-201 is more accurate than Tc-99m pyrophosphate in detecting and localizing acute myocardial infarction in patients without prior infarction and that Tc-99m pyrophosphate may fail to identify small infarcts. Infarct size can be estimated from the area of increased Tc-99m pyrophosphate uptake in patients with anterior infarction, but tends to be underestimated in patients with inferior infarction. Current techniques for imaging with Tl-201 permit differentiation between small, medium and large infarcts in patients without prior infarction but do not provide accurate measurement of the extent of acute myocardial infarction.

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The severity of an acute myocardial infarction and the patient's prognosis are related to the extent of acutely damaged myocardial tissue.[1] Furthermore, the site of infarction and the degree of mural involvement are important determinants of the left ventricular performance and early mortality.[2–4] Therefore, methods for reliably detecting, localizing and sizing acutely injured myocardium are desirable in order to select therapeutic interventions for limiting the extent of myocardial necrosis, thereby reducing infarct size and subsequent mortality. Although biochemical methods allow an estimate of the magnitude of myocardial damage once infarction has evolved, prediction of infarct size from the early increase in serum creatine kinase and other enzymes after infarction has not gained wide acceptance.[5,6] Recently, several noninvasive radionuclide techniques have been evaluated for visualizing acute myocardial infarction.[7–16] Imaging with technetium (Tc)-99m stannous (Sn) pyrophosphate is a sensitive means of detecting acute myocardial injury. Tc-99m pyrophosphate concentrates in acutely infarcted myocardium and delineates the region of infarction as a "hot spot." In contrast, potassium analogs accumulate in normal myocardium; perfusion abnormalities early during ischemic injury or in the area of a completed infarct are visualized as "cold spots" indicating regionally decreased or absent myocardial activity. Thallium-201 (Tl-201) has been utilized in the experimental animal and in man to demonstrate regions of diminished myocardial perfusion including regions with acute or recent myocardial infarction.[16,17] Tl-201 is suitable for imaging with the gamma scintillation camera and, because of its 72 hour physical half life, is more practical for clinical use than other short-lived potassium analogs.

Although both radionuclides, Tc-99m pyrophosphate and Tl-201, are considered useful for the scintigraphic diagnosis of acutely injured myocardium, their relative sensitivity in detecting acute myocardial infarction in relation to the biochemically measured extent of infarction and their usefulness in estimating infarct size have not been compared in man. This study was designed to examine these factors.

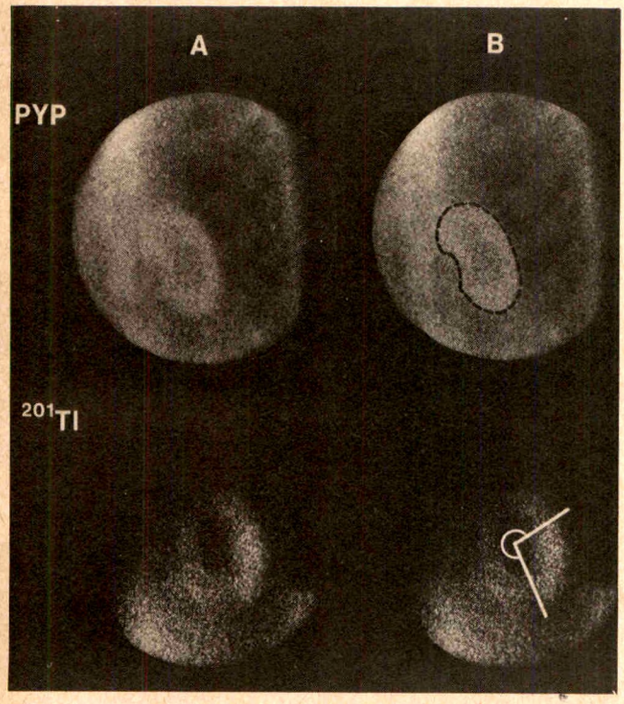


FIGURE 1. Myocardial images from a patient with acute anterolateral myocardial infarction. **Upper panel: A,** technetium-99m (Tc-99m) pyrophosphate (PYP) scintigram in the anterior projection with extensive radionuclide uptake showing centrally decreased tracer uptake. **B,** the scan shows the outlined Tc-99m pyrophosphate area in the largest projected view, which was used for scintigraphic infarct size measurement (see text). **Lower panel: A,** thallium-201 (^{201}Tl) image in the left anterior oblique projection showing a large area of decreased uptake in the anteroseptal, inferior and high lateral wall. **B,** the **white lines** demarcate the large sector of decreased Tl-201 uptake, which was estimated to the hearest 25 percent of the total left ventricular image and used for infarct size estimation (in this instance more than 50 percent) (see text).

Materials and Methods

Patients: Myocardial imaging was performed in 35 patients with an acute myocardial infarction admitted to the Ischemic Heart Disease Specialized Center of Research, University of California, San Diego. Twenty-four patients were men and 11 women, their ages ranging from 34 to 89 years (mean 59.5 years). The diagnosis of myocardial infarction was based on at least two of the following criteria: (1) a history of typical prolonged chest pain, (2) electrocardiographic changes indicative of myocardial injury with the subsequent evolution of a transmural infarction pattern, and (3) characteristic elevations of serum enzymes (creatine kinase [CK], glutamic oxaloacetic transaminase [GOT], lactic dehydrogenase [LDH]). Subendocardial infarction was diagnosed on the basis of typical S-T and T wave depression accompanied by both criteria 1 and 3. Electrocardiographically the site of transmural infarction was anterior in 8 patients, anterolateral in 10, lateral in 4 and inferior in 13. In the 13 patients with an inferior wall infarction, the electrocardiogram indicated additional transmural lateral wall involvement in two and posterior wall involvement in one. Four patients had a subendocardial infarction and six had a documented previous myocardial infarction. At the time of study, one patient had right bundle branch block and one had left anterior hemiblock; all patients had sinus rhythm. Each patient gave written informed consent before study.

Tc-99m pyrophosphate scintigrams: Tc-99m pyrophosphate images were obtained 22 to 113 hours (mean 2.7 days) after the onset of acute symptoms of myocardial infarction. Imaging was performed 2 hours after intravenous injection of 15 mCi of Tc-99m pyrophosphate using a gamma scintillation camera (Pho Gamma HP, Searle Radiographics, Inc.) equipped with a low energy high resolution parallel hole collimator. Views included the anterior, 45° left anterior oblique and left lateral projections, and 400,000 counts were collected for each image. All scintigrams as well as a grid of known dimensions were recorded on Polaroid® film and examined independently by two observers without knowledge of the patient's clinical and laboratory findings. The intensity of Tc-99m pyrophosphate uptake was graded from 0 to 4+ using a modified version of the classification described by Parkey et al.[7] Zero represented no activity, 1+ questionable activity, 2+ definite activity with an intensity equal to that of the ribs, 3+ increased activity compared with that of the ribs and 4+ activity equal to or exceeding that of the sternum. Scintigrams with 0 or 1+ precordial activity were considered

normal and those with 2+, 3+ and 4+ activity with the region of uptake seen on at least two views were considered abnormal. For infarct sizing, the scintigram showing the largest area of Tc-99m pyrophosphate uptake was selected and magnified and the area of Tc-99m pyrophosphate uptake outlined. The largest area of abnormal uptake in each patient was then determined with planimetry and, with use of a grid of known dimensions, expressed in square centimeters (Fig. 1). The mean value of the two calculated areas was used when the measurements of the two observers differed.

Tl-201 scintigrams: Within 10 to 22 hours after completion of the Tc-99m pyrophosphate studies (that is 2 to 6 days [mean 3.5 days] after the onset of acute symptoms) myocardial imaging using Tl-201 was performed. None of the patients had electrocardiographic or enzyme changes suggestive of infarct extension between the two radionuclide studies. Two mCi of Tl-201* as thallium chloride dissolved in 2 to 3 ml of saline solution was injected intravenously. Precordial images were recorded with the same gamma camera and collimator used for Tc-99m pyrophosphate imaging. A 20 percent window set around the 60 to 90 Kev mercury X-ray photons was used. Imaging was begun 30 to 90 minutes after administration of Tl-201 in the same anterior, 45° left anterior oblique and lateral projections, with 400,000 counts recorded in each projection. The scintigrams were recorded on Polaroid® film for qualitative analysis. The Tl-201 images were analyzed for areas of decreased myocardial activity and compared with the electrocardiographic site of infarction and the location and extent of increased myocardial Tc-99m pyrophosphate uptake. In addition, each observer estimated the extent of decreased uptake to the nearest 25 percent of the total left ventricular myocardial image. The defects were classified as small, medium and large according to the observer's estimate: small represented an area of decreased Tl-201 involving less than 25 percent of the left ventricular image, medium 25 to 50 percent and large more than 50 percent of the left ventricular image (Fig. 1).

Estimation of infarct size by serum CK curve analysis: A biochemical estimate of the extent of myocardial tissue damage was obtained in 24 patients using a creatine kinase (CK) curve analysis method.[6] Serum samples were collected for CK analysis at 2 hour intervals for 24 hours from the time of admission and every 4 hours thereafter until CK activity had returned to normal. CK curves were analyzed only in patients whose CK concentrations at the onset of the serum sampling period were within normal limits and who had no intramuscular injections or electrical countershocks.[18] CK activity was measured with Rosalki's method.[19] The completed serum CK curve was integrated and the fractional decay rate of enzymatic activity measured in each patient. The CK curve area was expressed in international units per liter times hour (IU/liter·hour). Among the 24 patients whose infarct size was assessed with CK curve analysis, the electrocardiogram revealed an anterior or lateral infarction in 14 and inferior wall involvement in 10.

Analysis of results: Each observer evaluated the scintigrams obtained with the two radionuclides with respect to area of myocardial Tc-99m pyrophosphate uptake and decrease in Tl-201 myocardial activity and compared the results with the electrocardiographic site of infarction. Localization of abnormal Tc-99m pyrophosphate uptake also was compared with that of Tl-201. The areas of Tc-99m pyrophosphate uptake were correlated with the biochemical estimates of myocardial damage, using the largest scintigraphic area of uptake from one of the three views and the area assessed with the completed CK curve. Gradations of the extent of reduced Tl-201 uptake were compared with the CK estimate of infarct size and the largest area of Tc-99m pyrophosphate uptake.

Calculations of linear regression, correlation coefficients and P values with standard t testing were performed on an XDS Sigma 3 computer.

* Kindly supplied by New England Nuclear Corporation, North Billerica, Massachusetts.

Results

Interobserver variability: There was good agreement between both observers in evaluation of the scintigrams with respect to visualizing myocardial Tc-99m pyrophosphate uptake and decreased regional uptake of Tl-201 and in determining the location of abnormal or decreased uptake of radionuclide. However, in three patients with abnormal Tc-99m pyrophosphate scintigrams, lateral extension was interpreted by only one observer, and in one patient with an inferior infarction on electrocardiography the uptake was interpreted as inferolateral by one observer and inferoapical by the other. Similarly, in two Tl-201 myocardial images, an additional area of decreased radionuclide uptake in the lateral and the inferior wall, respectively, was detected by one observer only. In two other instances, defects in addition to an anterior infarct were localized to the apical wall by one observer and to the lateral wall by the other observer. When there was disagreement on scintigraphic area of abnormal radionuclide uptake, the observers reevaluated the images together and reached a consensus. There was a good correlation between observers in grading the intensity of Tc-99m pyrophosphate uptake ($r = 0.96$), and all scintigrams interpreted as normal (0 or 1+) by one observer were also graded as 0 or 1+ by the other. There was also good agreement in outlining and measuring the area of Tc-99m pyrophosphate uptake ($r = 0.96$); the observers' measurements of the area of radionuclide uptake never differed by more than 15 percent.

Detection and localization of acute myocardial infarction by Tc-99m pyrophosphate and Tl-201: Correlation with electrocardiogram: The results of the two radionuclides used in the same 35 patients in detecting acute myocardial infarction are shown in Table I. Five of the 35 patients (14.3 percent) with a

TABLE I

Detection and Localization of Myocardial Infarction With Tc-99m Pyrophosphate and Thallium-201 in 35 Patients With Acute Myocardial Infarction

	Tc-99m Pyrophosphate	Thallium-201
Abnormal scans	30 (85.7%)	35 (100%)
Normal scans	5 (14.3%)	0
Location of infarct on scan		
Corresponding to ECG infarct site	23/30 (76.7%)	33/35 (94.3%)
Not corresponding to ECG infarct site	7/30 (23.3%)	2/35 (5.7%)
Additional location of PYP uptake or TL defect	9/30 (30%)	16/29 (55.2%) *18/35 (51.4%)

*Including patients with prior myocardial infarction.

ECG = electrocardiographic; PYP = Tc-99m pyrophosphate; TL = thallium-201.

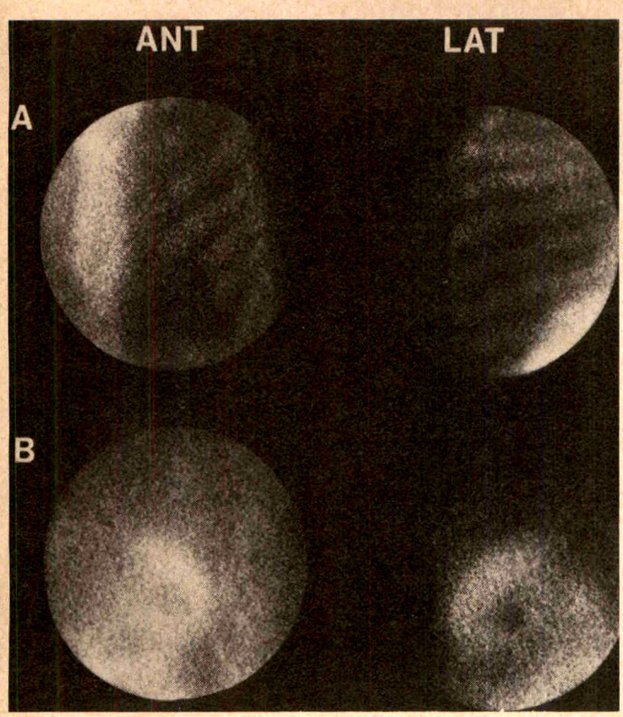


FIGURE 2. Scintigrams from a patient with acute transmural inferior myocardial infarction. **A,** normal Tc-99m pyrophosphate scans obtained 35 hours after the onset of acute symptoms. **B,** decreased uptake of thallium-201 is visualized in the anterior (ANT) and lateral (LAT) views.

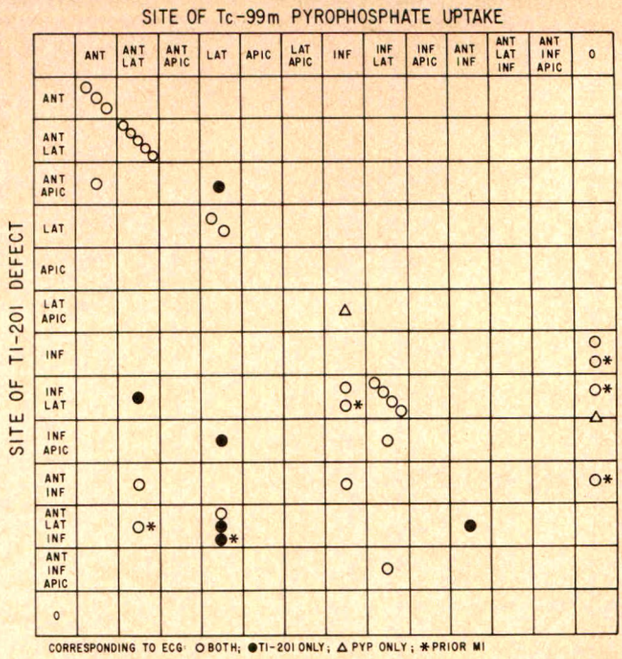


FIGURE 3. Correlation of the scintigraphic infarct location between Tc-99m pyrophosphate (PYP) myocardial uptake and decrease in myocardial Tl-201 uptake. Symbols at bottom indicate the correlation of the scintigraphic infarct localization with the electrocardiographic site of acute infarction. ANT = anterior; APIC = apical; ECG = electrocardiogram; INF = inferior; LAT = lateral; MI = myocardial infarction; O = negative.

definite myocardial infarction had a normal myocardial Tc-99m pyrophosphate image and two of these had a subendocardial infarction. In contrast, the Tl-201 images showed areas of decreased myocardial uptake in all 35 patients. In three of the six patients with a prior myocardial infarction, separate defects were noted in the Tl-201 images in areas corresponding to new Q waves and ST-T wave changes in the electrocardiogram. The three patients with a recurrent infarction electrocardiographically involving the same site as the previous infarction showed only one defect in the Tl-201 image. In one of these patients, this defect had become larger than that noted in a Tl-201 scintigram obtained 5 months earlier at the time of the first infarction. Figure 2 illustrates the scintigraphic findings in a patient with no previous infarction who had sustained an acute transmural inferior wall infarction with development of Q waves and serum CK elevations. No abnormal myocardial Tc-99m pyrophosphate uptake but a definite decrease in Tl-201 uptake was noted in the inferior wall and apex.

In 23 of the 30 patients (77 percent) with acute infarction and positive Tc-99m pyrophosphate images the scintigraphic location of the acute myocardial infarct correlated with the electrocardiographic site (Table I). An additional site of Tc-99m pyrophosphate uptake not suggested by the electrocardiogram was seen in nine patients (30 percent); it involved the lateral wall in six patients, the inferior surface in two and the anterior wall in one. By contrast, in 33 of the 35 Tl-201 myocardial images (94 percent), the location of decreased Tl-201 uptake corresponded to the electrocardiographic infarct site. However, in 16 of the 29 patients without prior myocardial infarction (55 percent), additional areas of decreased Tl-201 uptake were also detected. If one excludes defects that corresponded to sites of previous infarction, Tl-201 images exhibited additional abnormal areas in 17 of the 35 patients (49 percent). These areas were adjacent to the electrocardiographic infarct sites and were located in the inferior wall in six, the anterior wall in two, the lateral wall in three and the apex in seven patients, two of whom also had a lateral or anterior defect. In six patients, additional locations of increased myocardial Tc-99m pyrophosphate and decreased Tl-201 uptake were identical.

There was good agreement between the sites of Tc-99m pyrophosphate uptake and regions with reduced or absent Tl-201 uptake (*Fig. 3*), particularly when previous infarctions were excluded. In 8 of the 27 patients who had no prior infarction and abnormal myocardial scintigrams with both agents, the area of decreased Tl-201 uptake appeared larger than the area of Tc-99m pyrophosphate uptake, and the Tl-201 images detected a greater number of abnormal areas in these 8 patients, 4 of whom had an inferior infarction. In 17 patients, the area of decreased Tl-201 activity appeared equal to the area in the Tc-99m pyrophosphate image and in two patients with anterior and lat-

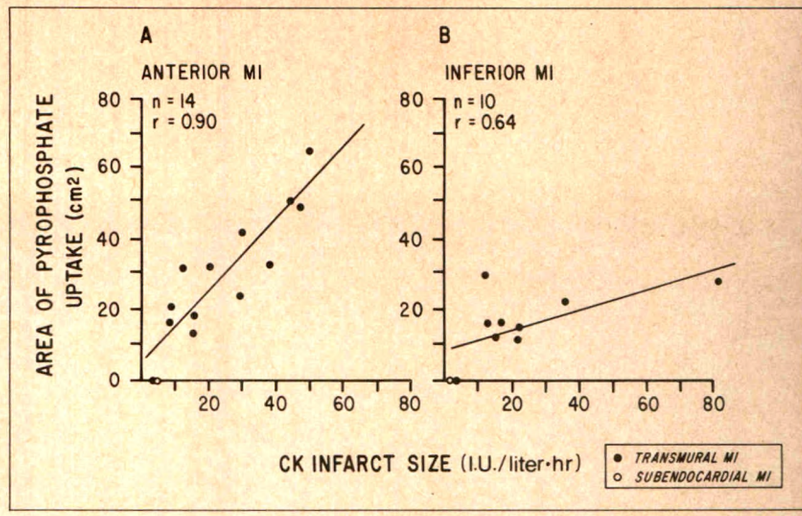


FIGURE 4. Relation between infarct size estimated from completed creatine kinase (CK) curves and the area of Tc-99m pyrophosphate uptake. **A,** there was good correlation between CK infarct size and scintigraphic infarct area in patients with anterior myocardial infarction (MI). **B,** this correlation was less good in patients with inferior infarction.

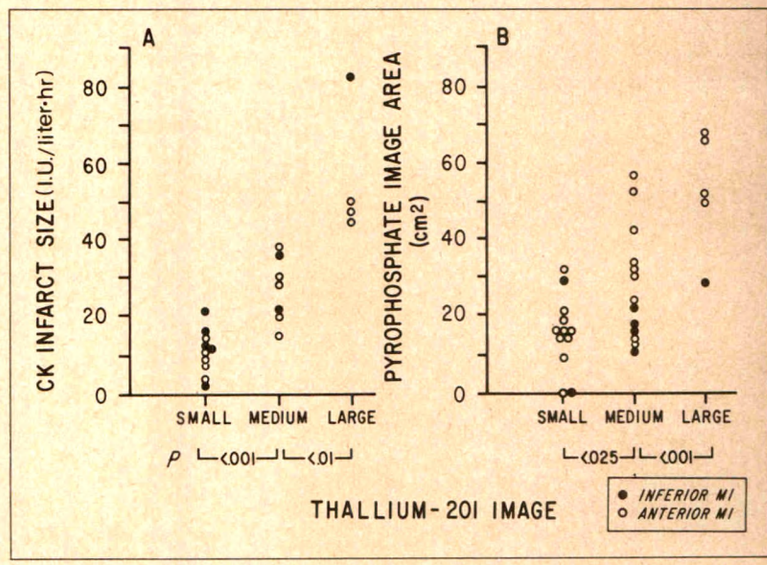


FIGURE 5. Relation between extent of decreased uptake of thallium-201 and infarct size estimated from creatine kinase (CK) curve analysis **(A)** and the scintigraphic infarct area of the Tc-99m pyrophosphate scan **(B).** CK infarct size separated the grades of decreased Tl-201 myocardial uptake well **(A);** no such separation is seen when the extent of decreased Tl-201 uptake is compared with the area of Tc-99m pyrophosphate uptake **(B).** MI = myocardial infarction; *P* = probability.

eral infarctions on electrocardiography the Tl-201 defect was smaller than the area of Tc-99m pyrophosphate uptake.

Sizing of infarct by myocardial scintigraphy and CK curve analysis: The largest measured area of myocardial Tc-99m pyrophosphate uptake in each case was correlated with infarct size as estimated with the completed serum CK curve analysis. For the 24 patients with completed CK curves, there was a positive correlation between the largest scintigraphic projection of infarct area and the infarct size determined from CK analysis ($r = 0.68$). This correlation improved considerably ($r = 0.90$) when the largest scintigraphic infarct area and CK infarct size were compared in the 14 patients with anterior, anterolateral or lateral wall myocardial infarction (Fig. 4A). However, this correlation was only fair ($r = 0.64$) in the 10 patients with inferior, inferoposterior or inferolateral wall infarction (Fig. 4B).

CK infarct size was determined in four of the five patients with normal Tc-99m pyrophosphate studies and in each instance was less than 5 IU/liter·hour, being smaller than the CK infarct size in patients who had definite abnormal Tc-99m pyrophosphate studies (Fig. 4, A and B). In all but one of the scintigrams obtained in patients with an anterior or anterolateral infarction the largest measured infarct area was obtained in the anterior or left anterior oblique view, and in 3 of the 13 patients with inferior infarction the lateral view projected the largest scintigraphic infarct area.

The results of the estimated size of the areas of decreased uptake in Tl-201 myocardial images are illustrated in Figure 5A. For the purpose of estimating the size of the infarct from the extent of decreased uptake, only patients without prior infarction and patients whose Tl-201 scintigrams showed a defect different from that of the previous site of infarct were included. Twelve patients had a small infarct, as estimated from

a decreased uptake involving less than 25 percent of the left ventricular myocardial image, 13 patients had a medium infarct with 25 to 50 percent involvement and 5 had a large defect involving more than 50 percent of the left ventricular image. When the data were compared with the infarct size estimated from CK curve analysis, there was separation of small, medium and large infarcts as determined from the Tl-201 image except in two patients with inferior and one with lateral infarction whose CK infarct size was within the lower range of the medium infarcts. The mean value for CK infarct size of 11.4 ± 1.9 (standard error) IU/liter·hour in the patients with a small infarct on Tl-201 imaging was lower than that in those with a medium infarct (27.2 ± 3.3 IU/liter·hour, $P < 0.001$). Similarly, the mean CK infarct size of 56.0 ± 8.7 IU/liter·hour in patients with a large infarct on Tl-201 imaging was greater than that in those with a medium infarct ($P < 0.01$).

The comparison of infarct size as estimated from Tc-99m pyrophosphate and Tl-201 images is illustrated in Figure 5B. The areas of myocardial Tc-99m pyrophosphate uptake showed wide ranges with overlap among the groups with small, medium or large infarcts as classified from the thallium images. Large infarcts had a larger average Tc-99m pyrophosphate area of 52.3 ± 7.0 (standard error) cm^2 when compared with medium and small infarcts (28.1 ± 4.1 cm^2 [$P < 0.001$] and 19.0 ± 2.2 cm^2 [$P < 0.001$], respectively). However, no significant difference existed between small and medium infarcts unless the two negative Tc-99m pyrophosphate scintigrams in the group with small infarcts were included (mean value of Tc-99m pyrophosphate image areas 15.9 ± 2.8 cm^2, $P < 0.025$).

Discussion

At present Tc-99m pyrophosphate and Tl-201 are used widely for assessing the extent of acute myocardial infarction or regional ischemia. The purpose of this investigation was to compare in patients both imaging techniques with respect to suitability for detecting, localizing and sizing acute myocardial infarction in relation to biochemically measured infarct size.

Sensitivity of Both Techniques in Detecting Acute Myocardial Infarction

Tc-99m pyrophosphate has previously been shown to identify reliably transmural and nontransmural myocardial infarction.[7,8,20] In this study of patients with electrocardiographically and enzymatically documented myocardial infarction, Tc-99m pyrophosphate images were positive in 86 percent. This value is similar to that reported by other investigators[21,22] but lower than the sensitivity reported by Willerson et al.[8] The time interval between the onset of acute symptoms and scintigraphy is unlikely to account for this difference because imaging was performed well within that period after infarction during which maximal uptake of Tc-99m pyrophosphate in infarcted myocardium reportedly occurs. Specifically, all patients with normal Tc-99m pyrophosphate images were studied between 24 and 62 hours after the onset of symptoms. The five normal studies included two in patients with an inferior wall infarction and two in patients with a subendocardial infarction. Since the inferior wall is oriented perpendicularly to the imaging plane, the distance between the inferior wall and the collimator is greater than that between the anterior wall and the collimator and faint uptake may be obscured by overlying ribs; therefore inferior infarcts would appear to be more difficult to visualize. Similarly, the amount of Tc-99m pyrophosphate accumulated in subendocardial infarctions may be too small to be detected by external imaging. This is further substantiated by the significant difference in infarct size (as determined from completed CK curves) between patients with normal and those with abnormal Tc-99m pyrophosphate images. Our results show that infarct size in patients with abnormal Tc-99m pyrophosphate studies averaged 26.9 ± 4.1 (standard error) IU/liter·hour, but only 3.2 ± 0.5 IU/liter·hour ($P < 0.02$) in patients with normal scintigrams. Tc-99m pyrophosphate failed to detect all infarcts of less than 5 CK-IU/liter·hour, but visualized all infarcts of more than 8 IU/liter·hour. Botvinick et al.[23] similarly have reported on a minimal infarct size for detecting experimental myocardial infarction in dogs with external imaging techniques. Detection of acute infarction with Tc-99m pyrophosphate imaging, therefore, may depend more on a critical size and location rather than a transmural or nontransmural site.

Differences between Tc-99m pyrophosphate and Tl-201 images: Whereas Tc-99m pyrophosphate accumulates primarily in irreversibly damaged myocardium,[24–27] Tl-201 concentrates in normal myocardium with its distribution closely following regional myocardial perfusion.[28] The regional decrease in myocardial Tl-201 activity, therefore, does not permit differentiation between perfusion abnormalities due to acute infarction, scar formation from previous infarction or ischemic regions that have not yet undergone necrosis. Defects in the myocardial Tl-201 images in patients with acute myocardial infarction therefore are likely to represent both zones of reversible ischemia and regions of irreversibly damaged myocardium. This may explain the findings in 30 percent of the patients, in whom the areas of decreased Tl-201 activity were larger than the areas of Tc-99m pyrophosphate uptake. Furthermore, in patients with negative pyrophosphate studies it is possible that the perfusion defects in the Tl-201 images primarily delineated ischemia rather than infarcted myocardium.

Although our results are consistent with those of most other investigations,[16,29] recent reports indicate a lesser sensitivity of Tl-201 myocardial imaging in diagnosing acute infarction.[30,31] It is possible that the greater sensitivity of Tl-201 imaging was, at least to some degree, related to the longer time interval between administration of Tl-201 and imaging. Imaging in this study was begun 30 to 90 minutes after injection of Tl-201. The decrease in blood and background activity during this period would appear to improve the diagnostic quality of the image. On the other hand, the accuracy of Tl-201 infarct imaging in this study was derived from a rela-

tively small number of patients. Subsequent Tl-201 scintigrams in 27 patients with definite myocardial infarction studied consecutively after completion of this investigation revealed two false negative studies, one in a patient with a nontransmural infarct and one in a patient with a transmural anterior infarct and left ventricular hypertrophy, indicating a revised sensitivity of 97 percent. Moreover, two patients in this group with a normal Tc-99m pyrophosphate scintigram and a previous infarct at the same electrocardiographic site as the acute insult had a single defect in the Tl-201 image; in one patient a Tl-201 image was not obtained at the time of the prior infarction. Thus, a new scintigraphic defect could not be separated from the old infarction and it is possible that the acute infarct, which was small on CK curve analysis, may not have been visualized in the absence of a prior infarction.

Possible extension in the size of infarction during the time interval between the Tc-99m pyrophosphate study and the subsequent Tl-201 study cannot be entirely ruled out as a cause of the different results with the two radionuclides. However, evidence from Wackers et al.[32] strongly indicates that extension of the observed defects occurs primarily within the first 24 hours. According to their report, Tl-201 defects decrease more often than increase in size during the same time interval used in our sequential studies with Tc-99m pyrophosphate followed by Tl-201. Moreover, none of our patients had enzymatic or electrocardiographic evidence of infarct extension. It therefore seems reasonable to conclude that there were no changes in the extent of infarction between the time of Tc-99m pyrophosphate and Tl-201 imaging to account for the greater sensitivity of Tl-201 imaging.

Comparison of both images with electrocardiographic location of infarct: With respect to location, perfusion deficits in the Tl-201 images agreed better with infarct location in the electrocardiogram than did the areas of myocardial Tc-99m pyrophosphate uptake. When compared with the electrocardiographic infarct site, additional locations of Tc-99m pyrophosphate uptake or Tl-201 defects were observed in 30 percent and 55 percent of the studies, respectively. In the majority of these patients these scintigraphic abnormalities were identical in location with both techniques. Similarly, in 63 percent of the abnormal studies obtained with both agents, the area of Tc-99m pyrophosphate uptake appeared equal to the region of decreased Tl-201 activity. Such similarity between the two techniques in delineating the extent of infarction may be explained by the ischemic border zone, which may take up Tc-99m pyrophosphate despite the only moderately decreased coronary blood flow to this area,[27] whereas such a hypoperfused zone may be included in the perfusion deficit of the centrally located infarct area.[28]

Estimation of Infarct Size by Tc-99m Pyrophosphate and Tl-201

Tc-99m pyrophosphate and CK curve analysis: Willerson et al.[33] have demonstrated previously a significant relation between the maximal area of Tc-99m (Sn) pyrophosphate uptake and the maximal serum CK elevation in patients with acute anterior infarction. However, maximal serum CK elevations do not take into account the rate and duration of myocardial CK release and bear only a rough correlation to the mass of infarcted myocardium when compared with the infarct size obtained from analysis of serial serum CK changes.[34] In our series reported here the correlation between the area of Tc-99m pyrophosphate uptake and infarct size in patients with infarction involving the anterior or anterolateral wall was poor ($r = 0.75$) when only maximal serum CK activity was used. However, use of the method of completed CK curve analysis indicated that the area of Tc-99m pyrophosphate uptake can provide an accurate estimate of infarct size in patients with acute anterior or anterolateral myocardial infarction ($r = 0.90$). A lesser correlation ($r = 0.64$) existed between the scintigraphic infarct area and infarct size determined by CK curve analysis in patients with inferior infarction. The size of inferior infarctions estimated by the radionuclide method was usually underestimated; that is, inferior infarcts had significantly smaller areas of Tc-99m pyrophosphate uptake (18.9 ± 2.5 cm^2 [standard error], $P < 0.03$) than anterior wall infarcts (33.2 ± 4.6 cm^2), whereas mean infarct size measured from the completed CK curve in anterior infarcts (23.4 ± 4.4 IU/liter·hour) did not differ from that in inferiorly located infarcts (22.3 ± 7.3 IU/liter·hour).

Nonuniform myocardial Tc-99m pyrophosphate uptake was observed in 10 of the 19 patients with acute anterior or anterolateral myocardial infarction and was characterized by a "doughnut" pattern, that is, a central decrease in Tc-99m pyrophosphate activity, a finding similar to that observed in animals with a large infarct after left coronary arterial occlusion.[24] In our study, the presence of a "doughnut" pattern was associated with larger CK infarct size (40.3 ± 4.5 IU/liter·hour) than that of infarct images in which a more uniform focal uptake was observed (16.8 ± 3.8 IU/liter·hour, $P < 0.005$). Similarly, the areas of Tc-99m pyrophosphate uptake in the presence of a "doughnut" pattern were significantly larger (49.8 ± 4.4 cm^2) than infarct areas with more uniform radionuclide uptake, which averaged 21.2 ± 2.9 cm^2 ($P < 0.001$). Thus, the appearance of a "doughnut" pattern suggests the presence of a large anterior myocardial infarction.

Tl-201 images and estimation of infarct size: Estimation of the extent of acute ischemic myocardial injury from the myocardial Tl-201 images revealed various difficulties. Imaging with Tl-201 does not permit differentiation of acute from previous infarction and the extent of the perfusion abnormality due to the acute infarct could be estimated only when separate defects were present or if scintigrams of the previous infarct were available. There are physiologic restraints to the accurate measurement of infarct size from the Tl-201 myocardial image. An altered perfusion pattern after acute myocardial infarction may include a marginal zone of ischemic yet viable tissue. Thus, scintigraphically detected perfusion abnormalities may not provide

accurate information regarding the extent of irreversible tissue damage. Indeed, the area of decreased Tl-201 uptake exceeded that of myocardial Tc-99m pyrophosphate uptake in one third of the patients. The often ill-defined edges of the regions with reduced Tl-201 uptake did not permit precise delineation of regions with reduced radionuclide uptake. Subjective assessment of the extent of Tl-201 perfusion defects allowed only a gross estimation of the infarct size as demonstrated by the correlation with infarct size by CK curve analysis (Fig. 5). However, when the gross estimate of the Tl-201 defect was compared with the area of Tc-99m pyrophosphate uptake, the wide range of the Tc-99m pyrophosphate areas did not permit separation of the groups categorized as having small, medium or large Tl-201 defects. Nevertheless, the mean values of the Tc-99m pyrophosphate infarct areas differed significantly between small and large and between medium and large Tl-201 defects. This finding is consistent with the suggestion of Parkey et al.[29] that Tc-99m pyrophosphate and Tl-201 images provide different information in evaluating the extent of myocardial damage in patients with acute infarction.

Computer techniques for quantifying regional myocardial Tl-201 activity may be ultimately required to obtain an accurate measurement of the perfusion abnormalities as an index of myocardial damage. There is evidence that the distribution of Tl-201 in myocardium is related, like that of potassium-43 (K-43), to regional perfusion,[28] and that myocardial uptake of K-43 correlates with both CK depletion and relative blood flow.[27] Thus, Tl-201 imaging may yet prove to be a valid means of measuring infarct size.

Clinical Implications

Scintillation camera imaging with either technique used in our study allowed detection and accurate localization of myocardial infarction. Although Tc-99m pyrophosphate imaging appeared less sensitive in detecting small acute infarcts, this imaging technique provided a rather accurate estimate of the extent of myocardial damage in anterior and lateral wall infarctions. On the other hand, Tl-201 imaging appeared to have extremely high sensitivity but lacks the ability to differentiate between reversible ischemia and irreversible myocardial injury or between a previous and an acute infarction. With the refinement and new development of imaging techniques, the combined use of "cold" and "hot spot" tracers may allow a more precise characterization of zones of ischemia and infarction and provide information about the perfusion and function of the remaining noninfarcted areas of myocardium and their relation to mortality and morbidity in patients with acute infarction.

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Left Ventricular Function in Patients With Coronary Arteritis Due to Acute Febrile Mucocutaneous Lymph Node Syndrome or Related Diseases

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Reports of a mucocutaneous lymph node syndrome that frequently affects the coronary arteries have been increasing in Japan and other countries including the United States. Twelve patients with a documented history of mucocutaneous lymph node syndrome or a related coronary arteritis were studied with right and left heart catheterization, cardiac output measurements, left cineventriculography and selective coronary arteriography. These patients were separated into two groups on the basis of coronary arteriographic findings. Group 1 comprised six patients with normal coronary arteriograms; group 2 included the remaining six patients with coronary arterial aneurysm or occlusion.

Left ventricular function differed in the two groups. It remained essentially normal in group 1 whereas decreased ejection fraction, increased end-diastolic volume, elevated end-diastolic pressure or mitral regurgitation were evident in four of the six patients in group 2. Two ventriculographic abnormalities were identified: (1) regional contraction abnormality secondary to myocardial infarction, and (2) generalized hypokinesia without electrocardiographic evidence of infarction, probably caused by myocarditis resulting from arteritis.

Two patients with severe coronary arterial obstruction and myocardial infarction underwent successful aortocoronary bypass grafting. Postoperatively both had patency of all grafts and one had improved left ventricular function. These experiences have first shown the feasibility and significance of surgical management for selected patients with coronary arterial lesions due to coronary arteritis caused by the mucocutaneous lymph node syndrome or related diseases.

Acute febrile mucocutaneous lymph node syndrome is a specific arteritis with a predilection for the main coronary arteries.[1–3] Although the clinical course of this disease appears to be more benign and self-limited in the majority of patients when compared with the almost always fatal course of infantile polyarteritis nodosa, the pathologic features of the coronary arteries in the two conditions are indistinguishable.[4,5] The pathogenesis of this peculiar syndrome remains unknown, but nearly 10,000 cases have been reported in Japan. The syndrome is predominant among Japanese children, but attention has been drawn to it by American pediatricians,[4,6] and reports of cases in various parts of the United States are increasing.[7–14] In addition, patients with a diagnosis of infantile polyarteritis nodosa or viral disease[15–18] have been reported to have features similar to those of patients with coronary arteritis due to the mucocutaneous lymph node syndrome.

Acute or late cardiac death occurs in 1 to 2 percent of patients affected by the syndrome, and aneurysm or obstruction (or both) of the major coronary arteries has consistently been demonstrated at autopsy in these

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TABLE I
Summary of Cases

Case no.	Age (yr) & Sex	Time of Study After Onset of Acute Illness	Electrocardiogram	Location of Coronary Arterial Aneurysm(A), Narrowing(N) or Obstruction(O)
		Group 1		
1	2 M	4 mo	Normal	...
2	2 M	1 mo	Normal	...
3	4 M	11 mo	Normal	...
4	7 F	10 mo	ST-T changes	...
5	2 F	1 mo	Normal	...
6	10 M	6 mo	LVH	...
		Group 2		
7	0.5 M	2 mo	Normal	LAD-A, LCx-A
8	9 M	2 yr, 4 mo	Normal	RCA-A, LAD-A
9	4 M	1 yr, 2 mo	Inferior MI	RCA-A & O
10*	4 M	11 mo	Anteroseptal MI	RCA-O, LAD-O, LCx-A
11	4 M	7 mo	LVH, ST-T changes	RCA-A, LMC-A, LCx-A
12*	26 M	12 yr	Anteroseptal MI	RCA-A & O, LMC-A, LAD-N

*Aortocoronary bypass grafting to left anterior descending and right coronary arteries.
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMC = left main coronary artery; LVH = left ventricular hypertrophy; MI = myocardial infarction; RCA = right coronary artery.

patients.[5] Moreover, coronary arterial lesions have frequently been demonstrated with coronary arteriography in surviving patients with a history of the syndrome.[2,3,19] Because the coronary artery is frequently involved, the function of the left ventricle may also be compromised. However, there are no reports on cardiac function in patients with coronary arteritis due to the mucocutaneous lymph node syndrome or related diseases. The purpose of this paper, therefore, is to describe left ventricular function and coronary arteriographic findings in 12 patients with a documented history of the mucocutaneous lymph node syndrome or with coronary arterial lesions resembling this syndrome. In addition, postoperative left ventricular function was studied in two patients who underwent double aortocoronary bypass grafting for their obstructive coronary artery disease.

Materials

Patients

This study group comprised 12 patients, 11 referred for cardiac evaluation because of an apparent history of acute febrile mucocutaneous lymph node syndrome fulfilling the diagnostic criteria proposed by the research committee.[1,2] Nine were male and two female; they ranged in age from 0.5 to 10 years. The remaining patient, who had an unknown febrile disease at age 14 followed by acute myocardial infarction at age 26 due to multiple coronary arterial aneurysms, was included in the study because of the close similarity of the lesions. All patients were studied after the acute stage of the disease had completely subsided as judged from clinical and laboratory findings at least 1 month after the onset of the illness.

Electrocardiograms at the time of the study in these patients were normal in six and showed ST-T segment abnormalities in two, left ventricular hypertrophy in two and abnormal Q waves compatible with old myocardial infarction in three. After recovery from the acute phase of the disease, all but three patients had no cardiac symptoms and were doing well. One of these three patients (Case 10) had a transient episode of cardiac arrest at the time of acute myocardial infarction and had very occasional anginal pain. A second (Case 11) required daily digoxin for the management of heart failure, and the third (Case 12) had exertional angina pectoris after myocardial infarction and limited exercise tolerance, requiring the prophylactic use of coronary dilators. Beta blocking agents were not used because of the borderline hemodynamic condition in this patient.

The 12 patients were classified into two groups according to the presence or absence of coronary lesions, such as aneurysm, narrowing or occlusion confirmed by selective coronary arteriography (Table I). Group 1 comprised six patients with normal coronary arteriograms and group 2 included six patients with lesions. Two patients in group 2 with a previous history of myocardial infarction due to obstruction of the coronary arteries underwent double aortocoronary saphenous vein bypass grafting to the left anterior descending and right coronary arteries.

All patients in this study received antibiotic drugs (mostly, penicillin derivatives) for almost the entire course of the acute illness; the use of these agents did not appear to affect the course of the disease significantly. During the acute phase of the disease, five patients (two in group 1 and three in group 2) were given corticosteroid treatment (average 2 mg/kg body weight of prednisone) although the value of steroid treatment is still controversial. Decisions to use steroid treatment depended on the clinical signs such as development of electrocardiographic abnormalities, cardiac enlargement and, primarily, gravity of the disease.

Methods

All studies were conducted with the patients at rest. Patients older than 7 or 8 years were given meperidine, 1 mg/kg intramuscularly, 1 hour before the study, and local anesthesia was added. Younger patients were given an intramuscular injection of ketamine for anesthesia.

Right and left heart catheterization was performed in all patients. Catheters were inserted through the femoral artery

and vein with the Seldinger method in most patients. In some patients younger than age 2 years an incision was made. Intracardiac pressures were measured using a Statham p23Db transducer connected with a catheter by way of a 20 cm hard wall Teflon® tube. Debubbling procedure was meticulously followed at each pressure measurement. The zero pressure reference was taken at the mid height of the thoracic cage. The first derivative of left ventricular pressure (dP/dt) was measured with an electric derivative. The pressure and dP/dt were photographed with a multichannel recorder. Cardiac output was measured with the dye-dilution method (indocyanine green) in eight patients after pressure measurements. Stroke volume by dye-dilution method was calculated by dividing cardiac output by heart rate.

Left cineventriculography was then performed using 35 mm film at 60 frames/sec in 10 patients. Nine of the 10 patients were studied in the 30° right anterior oblique position. The remaining patient had marked left ventricular dyssynergy and was studied in the right and left anterior oblique positions. Simultaneous electrocardiograms were superimposed on

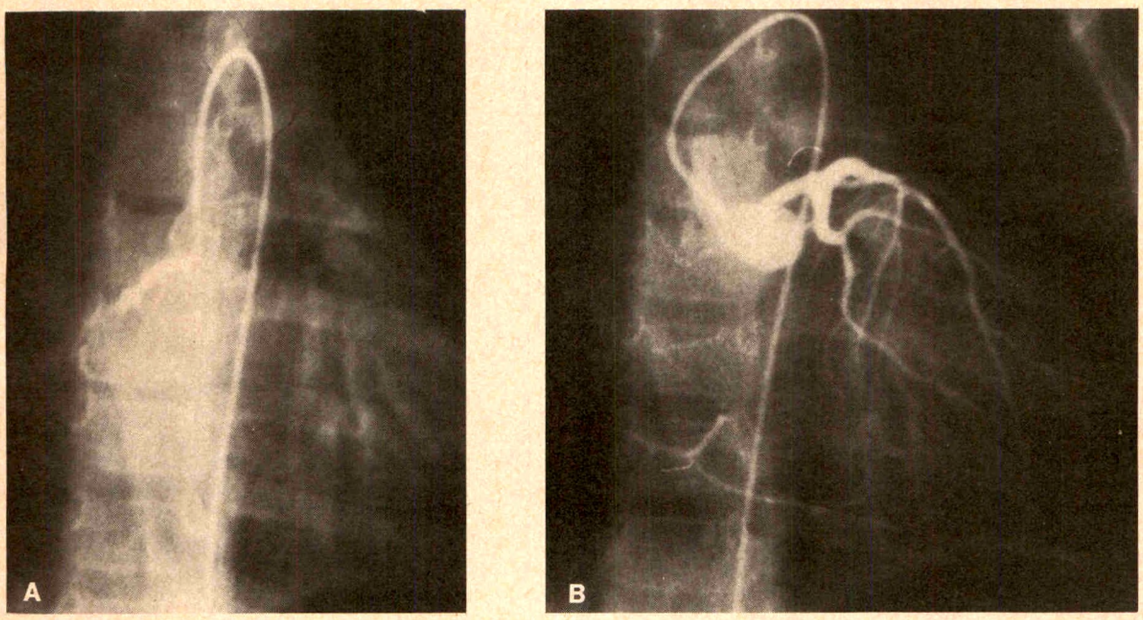


FIGURE 1. Case 9. Right **(A)** and left **(B)** coronary arteriograms. The right coronary artery has a small aneurysm that preceded a sudden total occlusion of the artery. Collateral flow occurs to the distal right coronary artery from the left coronary artery which appears normal.

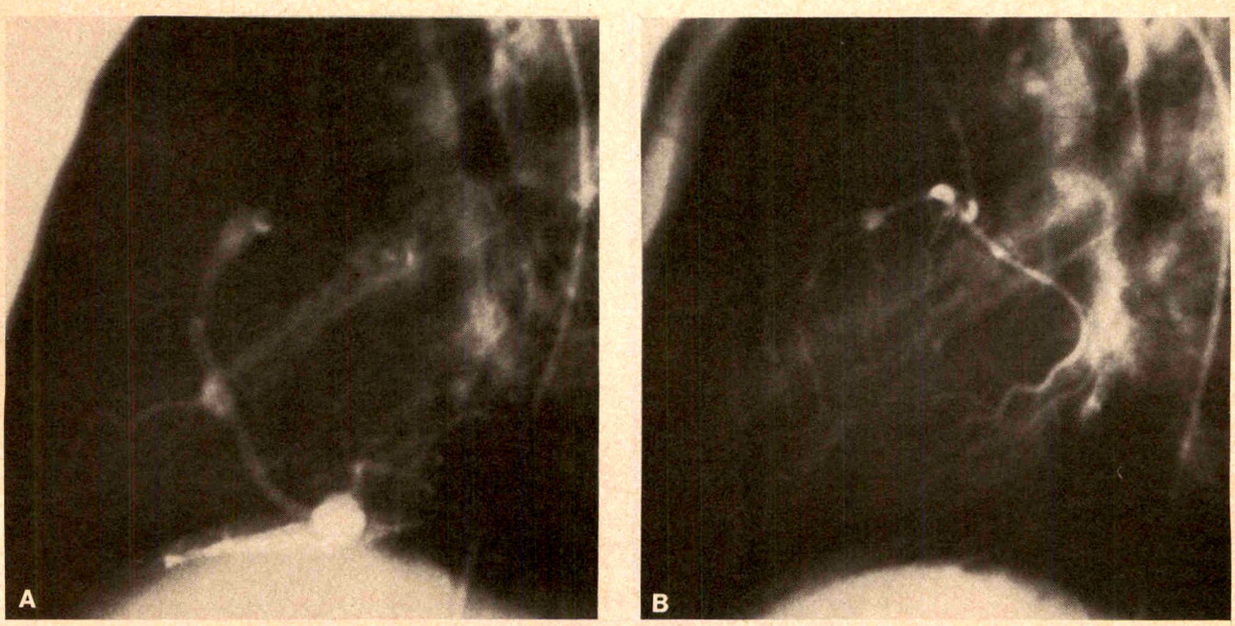


FIGURE 2. Case 8. Selective right **(A)** and left **(B)** coronary arteriograms. Multiple coronary arterial aneurysms are identified in both the right coronary artery (three aneurysms) and the left anterior descending coronary artery (one aneurysm). Neither dyssynergy of the left ventricle nor mitral regurgitation was present on ventriculography.

ventriculograms. In all patients, selective coronary arteriography was performed in at least two directions through the femoral artery. In the 11 children in the series, special catheters for selective coronary arteriography were handmade utilizing a no. 5 thin wall red catheter in the shape of a Judkins catheter. Catheters were preshaped to fit the aortic arch seen in the lateral chest X-ray film in each patient. Multidirectional selective coronary arteriography was successfully performed in all patients including a 6 month old child.

Left ventricular images were projected and traced on paper using a Tagarno 35 projector. Selection of images at different cardiac cycles was carried out visually and with use of electrocardiograms superimposed on cine films. Magnification of the view due to a nonparallel X-ray was corrected by using 1 cm^2 grids or a metal ball with a diameter of 3 cm, as reported previously.[20] A 12 inch (30.5 cm) image amplifier was used to encompass the entire left ventricle in one view. The end-diastolic and end-systolic volumes were measured using the area-length method, and corrected with the regression equation. The derived regression equation for our angiocardiographic systems was $Vc = 0.89\ Vm + 9$ ($r = +0.974$, $P < 0.001$), where Vc is a corrected volume and Vm a measured volume.[20] Angiographic stroke volumes and systolic ejection fraction were then calculated. Cardiac output and stroke volumes were normalized for body surface area.

Results

Angiographic Findings

Of the 6 patients with normal coronary arteriograms (group 1), none had significant dyssynergy of the left ventricle or mitral regurgitation on angiocardiography. The location of the coronary arterial aneurysm or the narrowing or obstruction (or both), in the six patients of group 2 is listed in Table I. Narrowing or obstruction (or both) of the major coronary arteries was associated with an aneurysm in three patients. All three patients had a documented history and electrocardiographic evidence of acute myocardial infarction of the anteroseptal wall (two patients) or inferior wall (one patient).

Left ventriculography in two patients with anteroseptal infarction revealed the presence of dyssynergy: anteroapical hypokinesia in one (Case 10) and anteroapical akinesia of 22 percent of the end-diastolic left ventricular circumference in one (Case 12). The latter patient also had mild mitral regurgitation. These two patients with severe coronary arterial obstruction and anteroseptal infarction underwent insertion of double aortocoronary bypass grafts that were patent on postoperative graft angiography. Detailed data on these patients were reported elsewhere.[19,21] The remaining patient (Case 9) had an inferior myocardial infarction due to total occlusion of the right coronary artery (Fig. 1) and had nearly normal contraction of the left ventricle.

In the other three patients of group 2, obstructive coronary arterial lesions were not demonstrated on angiography although the presence of definitive coronary aneurysm was apparent. In one of these three patients (Case 8) the contraction pattern of the left ventricle was normal and the chamber was of normal size despite the presence of multiple aneurysms in the left anterior descending and right coronary arteries (Fig. 2). This patient had no mitral regurgitation. In the remaining two patients, mitral regurgitation probably due to papillary muscle dysfunction was demonstrated on left ventriculography. One patient with mitral regurgitation (Case 11) had a greatly enlarged left ventricle associated with large aneurysms in the right and left coronary arteries (Fig. 3 and 4). The left ventricle was

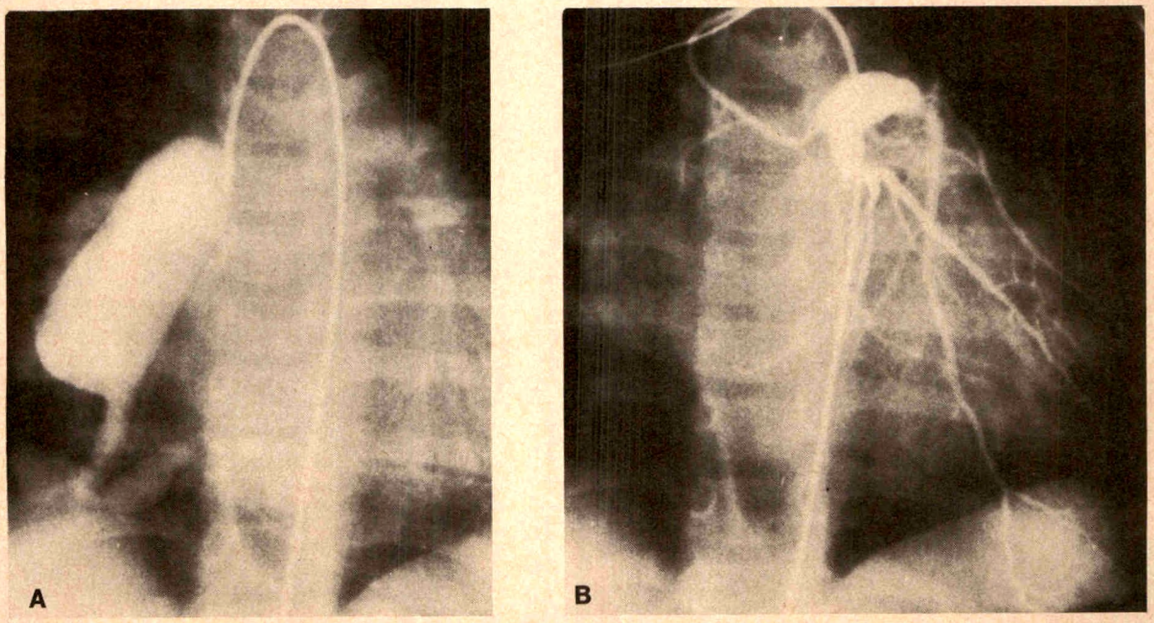


FIGURE 3. Case 11. Selective coronary arteriograms. **A,** a huge aneurysm is present in the right coronary artery extending from its orifice to its mid portion. There is also a diffuse dilatation of this artery down to the crux. Some clots are seen in the aneurysm. **B,** large aneurysmal formation in the left main coronary artery extending into the origin of the circumflex artery. Despite the large aneurysms in both coronary arterial systems, no apparent obstruction was identified.

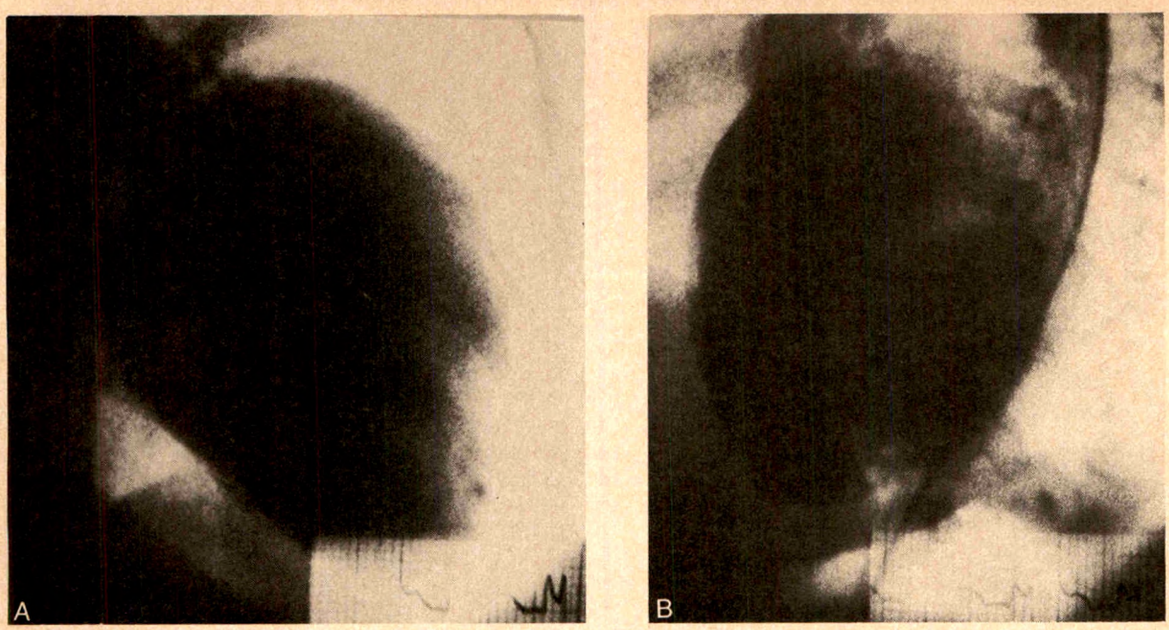


FIGURE 4. Case 11. Left ventriculograms in the right **(A)** and left **(B)** anterior oblique positions. The left ventricle is greatly enlarged with generalized hypokinesia. The end-diastolic volume was computed to be 225 ml (326 ml/m^2) and the ejection fraction was 0.2. A moderate grade of mitral regurgitation was combined.

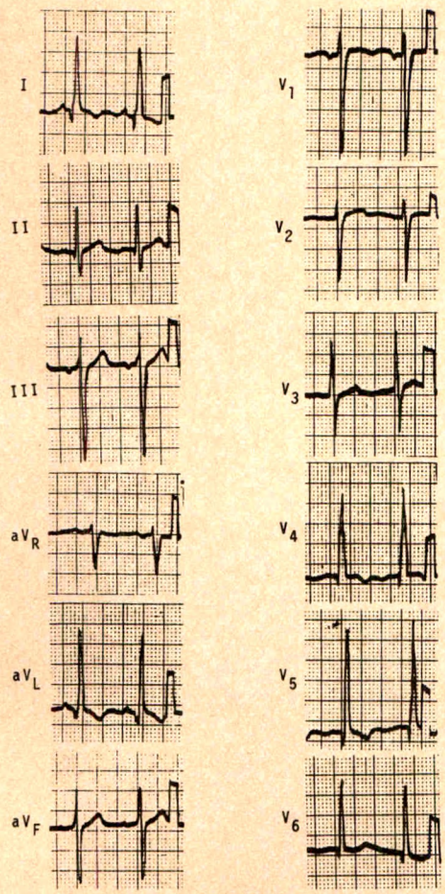


FIGURE 5. Case 11. Electrocardiogram in the same patient. Although small Q waves are seen in leads I, aVL, V_4 and V_5, there are no signs compatible with a large transmural infarction. The ST-T segment changes associated with left ventricular hypertrophy ($SV_1 + RV_5 = 47$ mm) are evident.

extremely enlarged with an end-diastolic volume of more than 300 ml/m^2, and ventricular contraction was diffusely impaired with an ejection fraction of only 0.2. However, there were no apparent electrocardiographic signs of a large myocardial infarct (Fig. 5). Myocarditis was considered the cause of this patient's generalized impairment of myocardial contraction although pathologic data were not available. In another patient with mitral regurgitation (Case 7), multiple aneurysms of the left anterior descending and circumflex coronary arteries were demonstrated (Fig. 6). No electrocardiographic evidence of infarction was identified in this patient.

Hemodynamic Results (Table II)

In the six patients with normal coronary arteriograms (group 1), all hemodynamic variables were within normal limits. The cardiac index ranged from 4.27 to 6.76 liters/min per m^2 (mean 5.08) (Fig. 7). The left ventricular end-diastolic pressure was 6 to 8 mm Hg (average 7.5) (Fig. 7). The maximal dP/dt ranged from 1,100 to 1,800 mm Hg/sec (average 1,460). The end-diastolic volume ranged from 54 to 86 ml/m^2 (average 66) (Fig. 8) and the ejection fraction ranged from 0.62 to 0.71 (average 0.66) (Fig. 8).

In the six patients with coronary arterial lesions (group 2), the cardiac index was within normal limits (range 2.78 to 4.97 liters/min per m^2, average 3.81) (Fig. 7). The left ventricular end-diastolic pressure ranged from 5 to 25 mm Hg (mean 12) (Fig. 7). In two patients, one with a large myocardial infarct and the other with diffuse hypokinesia associated with an enlarged left ventricle, the end-diastolic pressure was elevated to 25 and 16 mm Hg, respectively. The maximal dP/dt was 1,200 to 1,450 mm Hg/sec (average 1,340). The end-diastolic volume was distributed widely between 65 and

TABLE II

Hemodynamic Data

Case no.	BSA	HR	Pressures (mm Hg) Ao	PA	LVEDP	dPdt max	CI	SI_d	EVD	ESV	SI_a	EF	MR
					Group 1								
1	0.58	108	92/70(75)	12/6(8)	8	...	...	...	...	...	...	...	—
2	0.53	115	98/68(80)	18/9(13)	8	1800	...	...	...	...	...	...	—
3	0.68	117	82/38(50)	13/6(9)	6	1700	4.85	41	63	22	41	0.65	—
4	0.84	110	80/53(68)	27/10(15)	8	1100	4.27	39	61	20	41	0.67	—
5	0.55	144	80/44(60)	20/6(10)	7	1300	6.76	47	54	16	38	0.71	—
6	0.96	76	130/70(94)	23/13(16)	8	1400	4.42	58	86	33	53	0.62	—
Mean		112	94/57(71)	18/8(12)	7.5	1460	5.08	46	66	23	43	0.66*	
					Group 2								
7	0.37	154	85/56(70)	25/13(17)	10	...	...	...	73	38	35	0.48	+
8	1.04	102	110/76(90)	19/9(11)	7	1450	4.97	49	65	22	43	0.66	—
9	0.64	138	122/62(82)	28/10(14)	5	1300	3.29	24	70	23	47	0.67	—
10													
Pre	0.66	96	82/38(54)	16/7(10)	8	...	4.22†	...	97	53	44	0.45	—
Post		90	88/38(58)	14/5(9)	4	1350	5.58†	...	101	39	62	0.61	—
11	0.69	156	88/62(73)	32/15(20)	16	1400	3.79	25	326	262	64	0.20	+
12													
Pre	1.80	58	96/68(80)	34/20(24)	25	1200	2.78	48	119	70	49	0.41	±
Post		80	104/68(82)	25/10(18)	15	1350	2.58	32	130	78	52	0.40	+
Mean‡		117	97/60(75)	26/12(16)	12	1340	3.81	36	125	78	47	0.48*	

*$P < 0.05$.
†By angiographic method.
‡Excluding postoperative data.
+ = present; — = absent.

Ao = aortic pressure (systolic/diastolic [mean]); BSA = body surface area (m^2); CI = cardiac index (liters/min per m^2); dP/dt max = maximal rate of rise of left ventricular pressure (mm Hg/sec); EDV = left ventricular end-diastolic volume (ml/m^2); EF = left ventricular ejection fraction; ESV = left ventricular end-systolic volume (ml/m^2); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure; MR = mitral regurgitation; PA = pulmonary arterial pressure (systolic/diastolic [mean]); Post = postoperative; Pre = preoperative; SI_a = stroke volume index by angiographic method (ml/m^2); SI_d = stroke volume index by dye-dilution method (ml/m^2).

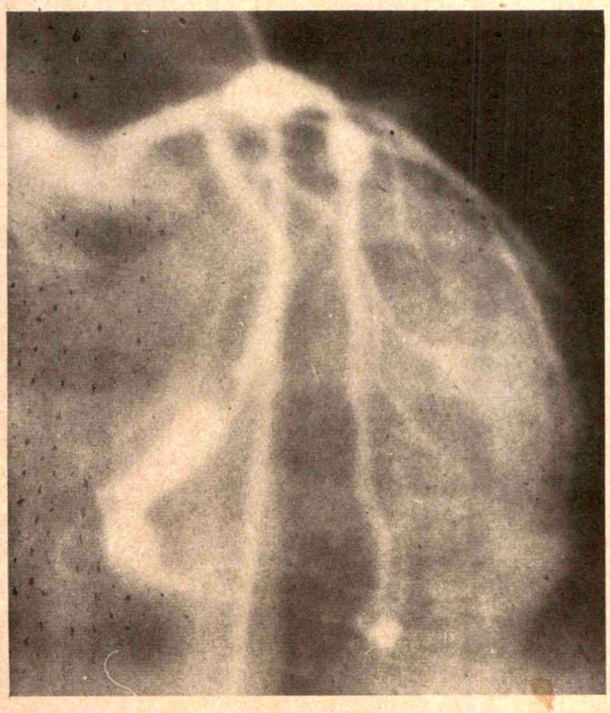


FIGURE 6. Case 7. Left coronary arteriogram. Multiple coronary arterial aneurysms are present in the left anterior descending and circumflex arteries. There was moderate mitral regurgitation on ventriculography. No electrocardiographic evidence of myocardial infarction was identified.

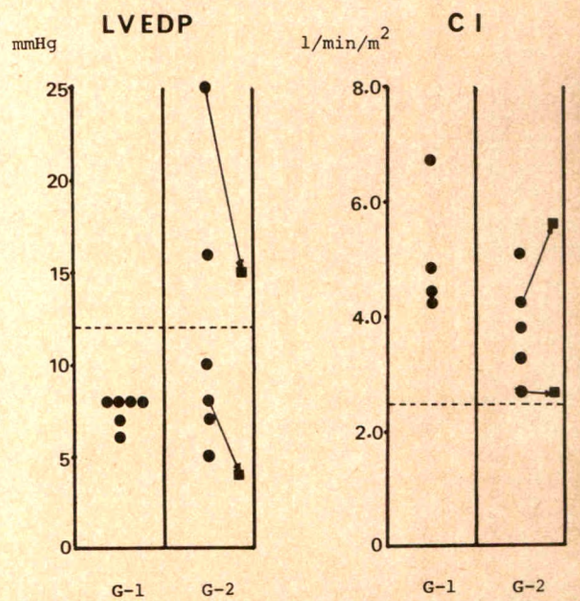


FIGURE 7. Left ventricular end-diastolic pressure (LVEDP) and cardiac index (CI) in patients in groups 1 (G-1) and 2 (G-2). The left ventricular end-diastolic pressure was elevated in two patients in group 2, one (Case 12) with myocardial infarction and the other (Case 11) with generalized hypokinesia and a greatly enlarged left ventricle. The cardiac index was within normal limits in all patients in both groups. **Closed circles** and **squares** indicate values before and after operation, respectively. The **dotted line** separates normal from abnormal values.

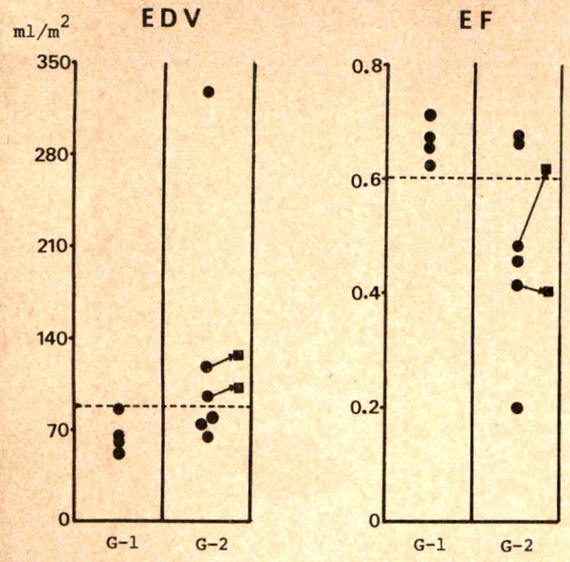


FIGURE 8. Left ventricular end-diastolic volume (EDV) and ejection fraction (EF) in patients in groups 1 (G-1) and 2 (G-2). The end-diastolic volume was increased in three patients in group 2, two with previous myocardial infarction and one with generalized hypokinesia associated with mitral regurgitation (Case 11). No significant changes were observed in end-diastolic volume before and after operation in two patients (Cases 10 and 12). The ejection fraction was lower than 0.5 in four of the six patients in group 2. The ejection fraction improved significantly in one patient (Case 10) after aortocoronary bypass grafting. **Closed circles** and **squares** indicate values before and after operation, respectively. The **dotted line** separates normal from abnormal values.

326 ml/m^2 (mean 125). Two of the three patients with an increased end-diastolic volume (more than 95 ml/m^2) had a previous myocardial infarct; the remaining patient had generalized hypokinesia of the left ventricle (Fig. 8). The ejection fraction ranged from 0.20 to 0.67 (average 0.48). Four of the six patients had a decreased ejection fraction of less than 0.5. The decrease in ejection fraction in group 2 was significant when compared with the values in group 1 ($P < 0.05$). In the two patients with successful aortocoronary bypass grafting, the ejection fraction increased postoperatively (from 0.45 to 0.61) in one and showed no improvement (from 0.41 to 0.40) in the other. In the latter patient, the preoperatively elevated end-diastolic pressure decreased from 25 to 15 mm Hg postoperatively, accompanied by the identical change in pulmonary arterial pressure. In both of these patients postoperative graft angiography demonstrated widely patent grafts. Figure 9 shows a classification of the 12 patients studied according to the coronary arteriographic and left ventriculographic findings.

Follow-up Studies

All six patients in group 1 were asymptomatic and could lead a normal life for their age at the time of study (at least 1 month after the acute episode had completely subsided); all remained symptom-free for at least 5 months after the study. None of the six had repeat angiographic studies.

Three patients in group 2 (Cases 7, 8 and 9) were symptom-free at the time of study although one had a documented history of inferior infarction with occasional premature ventricular contractions thereafter. They remained in the same clinical condition, and did not undergo repeat angiographic studies. One patient (Case 11) underwent repeat coronary and left ventricular angiographic studies after a 6 month interval; the procedures demonstrated a slight decrease in size of the right coronary arterial aneurysm although it was still extremely large (Fig. 3a); there was no change in the left coronary arterial aneurysm or the pattern of left ventricular contraction. This patient had decreased exercise tolerance, requiring the continual use of digoxin, but no angina pectoris.

Two patients with bypass operation[19,21] showed clinical improvement and were doing well 1.5 (Case 10) and 2.5 years (Case 12) postoperatively. The latter patient had mild exertional angina postoperatively. Angiographic studies, repeated three times in this patient, showed consistently patent bypass grafts to the left anterior descending and right coronary arteries. The left coronary arterial aneurysm from which the nondominant circumflex artery originated was found to be thrombosed without any signs of infarction. An additional small aneurysm in the periphery of the right coronary artery was demonstrated postoperatively with graft angiography; it had not been visualized preoperatively because of the total occlusion of this vessel near the orifice.[21] The contraction pattern of the left ventricle remained essentially the same after operation in this patient, but the angina pectoris was significantly alleviated and became easily controlled with the occasional use of nitroglycerin. The other surgically treated patient (Case 10) was leading a completely normal life and growing normally without cardiac problems postoperatively. Postoperative improvements of the angiocardiographic findings associated with well functioning grafts were documented.[19]

Discussion

The pathologic findings in autopsy cases of coronary arteritis due to the mucocutaneous lymph node syndrome are not distinguishable from those of infantile polyarteritis nodosa.[4,5] In addition, coronary arteriographic findings in surviving children in the United States with a history of polyarteritis nodosa[15,16] resemble those of patients in Japan with the mucocutaneous lymph node syndrome. Other reported cases of coronary arterial aneurysm or obstruction in children[18,22] may have been due to a related disease. The mucocutaneous lymph node syndrome has now been reported from all areas of the United States[7–14] as well as from Korea, Greece and Canada.[23–25] Thus, the mucocutaneous lymph node syndrome, infantile polyarteritis nodosa and other coronary arteritis in children that has been reported to have a viral origin may be similar diseases with a worldwide distribution although the incidence of the disease may differ greatly in different places.

Although the etiology of the mucocutaneous lymph node syndrome is not established, it is apparent that the disease has an extraordinary tendency to involve the

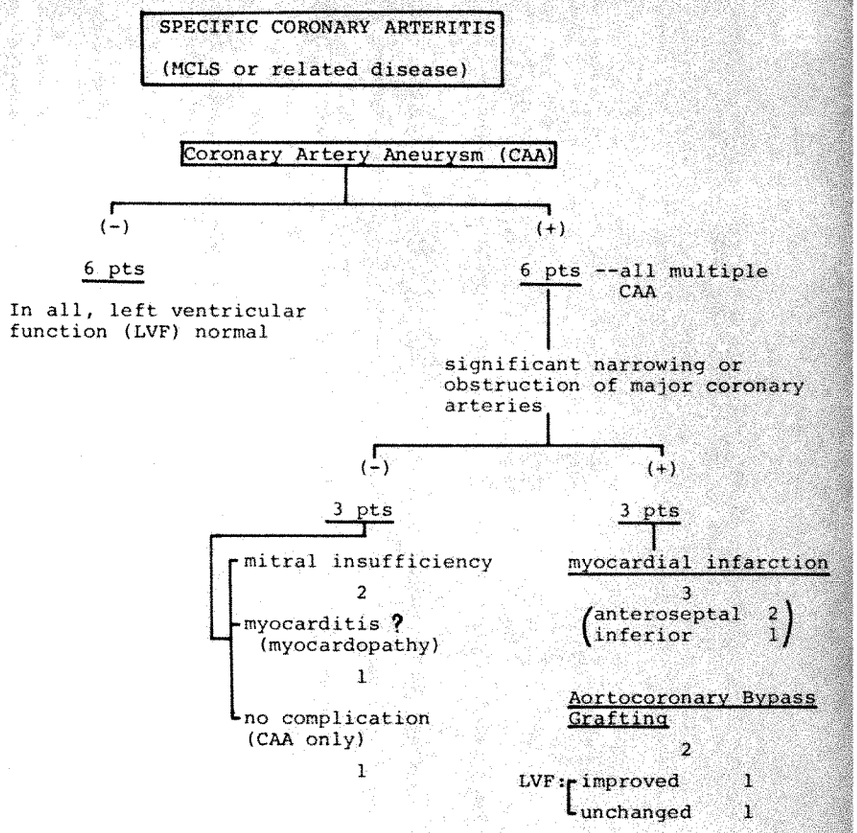


FIGURE 9. Schematic classification of 12 patients with the mucocutaneous lymph node syndrome (MCLS) or related disease studied with cardiac catheterization, left ventriculography and selective coronary arteriography. A distinct relation was noted between the presence of coronary arterial aneurysms (CAA) and impairment of left ventricular function (LVF). pts = patients.

main coronary arteries. Therefore, the possibility exists that it can also compromise left ventricular function as a process of the disease or as a consequence of the coronary arterial involvement. However, there are no reports available on cardiac function in patients with coronary arteritis due to the mucocutaneous lymph node syndrome or related diseases.

Left ventricular dysfunction and contraction abnormalities: In our 12 patients there was a distinct relation between the presence of coronary arterial aneurysms and impairment of left ventricular function. At the time of the study no patient in group 1 had significantly impaired ventricular function. In contrast, of the six patients with coronary arterial aneurysms and obstruction (group 2), two had mitral regurgitation, three had myocardial infarction and four had abnormal left ventricular function, as manifested particularly by the ejection fraction. Two types of derangement of the pattern of left ventricular contraction were identified. The first type, evident in two patients, was a regional contraction abnormality secondary to myocardial infarction that resulted from thrombotic or embolic occlusion of the coronary artery. In both patients the presence of myocardial infarction and coronary arterial obstruction was proved with electrocardiography and coronary arteriography. The second type, seen in one patient, was a generalized contraction abnormality without apparent evidence of myocardial infarction, probably due to myocarditis as an extension of the inflammatory process involving the coronary arteries.

Our study indicates that the primary site of the mucocutaneous lymph node syndrome is the coronary arteries rather than the myocardium. After complete recovery from the acute illness, myocardial involvement significant enough to impair the pump function of the left ventricle was observed only in patients with coronary arterial lesions. Generalized impairment of myocardial function was also seen only in a patient with severe coronary arterial involvement. There was no evidence in this study that myocardial damage resulting in persisting significant functional abnormalities preceded the involvement of the coronary artery. Onouchi et al.[3] also reported that a persisting increase in cardiac silhouette was seen only in patients with coronary arterial aneurysms.

Aortocoronary bypass surgery: We have successfully performed double aortocoronary saphenous vein bypass grafting to the left anterior descending and right coronary arteries in two patients.[19,21] Surgical indications were based on both the clinical and the angiographic (anatomic) findings. One patient (Case 10) had an episode of transient circulatory arrest after acute myocardial infarction. After recovery he had occasional angina pectoris. Coronary arteriography demonstrated a total occlusion of the left anterior descending and right coronary arteries together with a small aneurysm in the circumflex artery, the only patent artery.[19] The other patient (Case 12) had a large infarct and limited exercise tolerance because of anginal pain, requiring the prophylactic use of nitroglycerin. Angiographic studies showed a large aneurysm located in the left main coronary artery together with total occlusion of the right

coronary artery and severe narrowing of the proximal left anterior descending coronary artery.[21] We believe that these life-threatening anatomic lesions in conjunction with the clinical findings including previous myocardial infarction warranted surgical intervention in these patients.

Kato et al.[2] reported the tendency of coronary arterial aneurysms to regress on serial coronary arteriographic studies. However, among our six patients in group 2, three had both coronary arterial obstruction and aneurysms, complicated by myocardial infarction. It is therefore difficult at present to predict which coronary arterial aneurysm will regress or become thrombosed and occluded in the future. However, it is unlikely that arteries, once totally occluded, later become widely patent, and there is no such reported evidence. In our patients surgery was considered only for severe obstructive lesions, not for the presence of a simple aneurysm.

In our two surgically treated patients, all bypass grafts were patent on postpostoperative examination, and the two patients are doing well 1.5 and 2.5 years, respectively, after operation. One patient had improved left ventricular contraction postoperatively, thus demonstrating that an ischemic contraction abnormality of the left ventricle is present in children with the mucocutaneous lymph node syndrome. The other patient, who had a large anteroapical akinetic area, manifested no improvement in left ventricular function although he had obvious amelioration of angina pectoris. These experiences are the first to reveal the feasibility and benefit of surgical treatment for carefully selected patients with inflammatory coronary arterial lesions in the mucocutaneous lymph node syndrome and possibly in those with related coronary arteritis. However, the number of cases and the follow-up periods are limited; therefore, the decision to perform surgery should be cautiously made.

Implications: It is possible that the child who has coronary arteritis due to mucocutaneous lymph node syndrome or related diseases may sustain myocardial infarction as an adult or may be found to have mitral regurgitation long after the acute episode subsided and is almost forgotten or neglected in the manner of measles or other viral infections. Some of the coronary arterial aneurysms or obstructions in patients sustaining myocardial infarction in early adulthood, mostly believed to be congenital in origin, may be a sequela of coronary arteritis in childhood. The clinical history and findings suggested that this was the situation in our Case 12 although there was no definitive pathologic confirmation.

The fate of the coronary arterial aneurysm due to coronary arteritis can be determined only with serial angiographic studies. We have successfully used handmade coronary arterial catheters for selective injection in each patient, including a 6 month old infant, and encountered no complications related to this method. The selective method is certainly preferable to aortic root injection of contrast material for accurate angiographic follow-up and is imperative in the selection of candidates for surgical management.

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Angiographic Diagnosis of Mitral Valve Prolapse: Correlation With Echocardiography

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Mitral valve prolapse is characterized clinically by a nonejection systolic click and a late systolic murmur and angiographically by end-systolic bulging of one or both mitral leaflets into the left atrium. If one accepts the end-systolic configuration of the left ventriculogram as the diagnostic standard, recent studies suggest that mitral valve prolapse may frequently be associated with certain other forms of cardiac disease. To determine the incidence of this finding in patients unselected for their primary cardiac diagnosis, the left ventricular angiograms from 336 consecutive patients (223 men and 133 women) were analyzed. Six patients had the clinical diagnosis of click-murmur syndrome, and all six had angiographic prolapse. Leaflet bulging was also present in 52 of 131 patients with ischemic heart disease (40 percent), 27 of 84 with rheumatic valve disease (32 percent), 3 of 19 with cardiomyopathy (16 percent), 5 of 12 with congenital heart disease (42 percent) and 50 of 84 with chest pain and no significant coronary artery disease (60 percent). Technically satisfactory echocardiograms were available from 140 of these patients; mitral valve prolapse was evident in the echocardiograms of 9 (6.4 percent), including 6 with the click-murmur syndrome.

Thus, angiographic mitral valve prolapse was present in 43 percent of cases and occurred without predilection for any diagnostic subgroup. Echocardiographic prolapse was less common but correlated well with the presence of the click-murmur syndrome. Some end-systolic bulging of posterior mitral leaflet scallops therefore is a common angiographic finding that should probably not be considered pathologic in the absence of other features of the click-murmur syndrome.

Barlow et al.[1] were first to demonstrate angiographically that patients with a nonejection systolic click and a late systolic murmur had mitral regurgitation, an abnormality subsequently shown to be due to systolic prolapse of one or both mitral valve leaflets into the left atrium.[2] Since their observations, numerous groups[3–16] have described the clinical, electrocardiographic, angiographic, pathologic and, recently, the echocardiographic features of this disorder. Although initial reports concerned patients with the typical auscultatory phenomena, the end-systolic configuration of the left ventricular angiogram has recently become accepted as the standard for diagnosis.[4,12] Use of this approach has led to the concept of "silent" mitral valve prolapse, that is, angiographic evidence of late systolic bulging of one or both mitral leaflets without the presence of a click or murmur.

Although recent information suggests that the click-murmur syndrome may be a relatively common disorder,[17,18] studies using angiographic criteria have indicated that mitral valve prolapse frequently occurs in patients with several other disease entities. Thus, angiographic prolapse, usually without a click or murmur, has been reported in 37 percent of patients with secundum atrial septal defect,[19] 32 percent of

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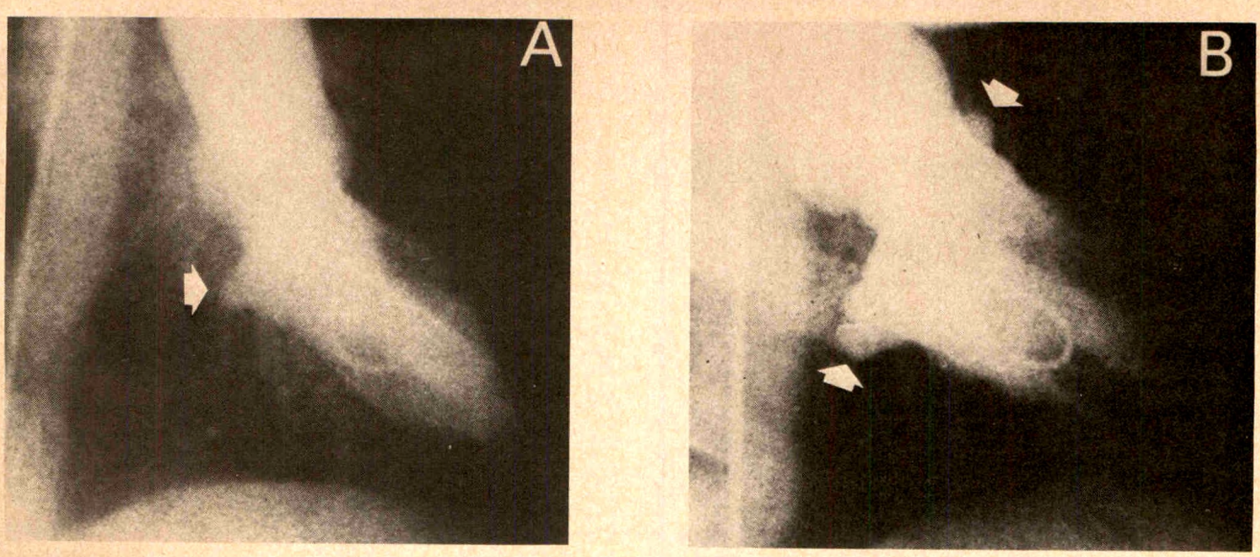


FIGURE 1. End-systolic frames (right anterior oblique projection) from the left ventricular angiograms of two patients. **A, arrow** indicates the small but definite bulge of the posteromedial commissural scallop in a patient judged to have grade 1 mitral valve prolapse. **B, arrows** indicate the large posteromedial and smaller anterolateral scallops in a patient assessed as having grade 3 angiographic prolapse. There is also a bulge in the region of the medial scallop. Note the much larger volume of the prolapsed scallops in **B** compared with those in **A.**

patients with critical coronary artery disease[20] and 25 percent of patients with chest pain and normal coronary vessels.[21] The diverse nature of these conditions does not suggest a common pathogenesis of mitral valve dysfunction, thus creating doubt concerning the specificity of the angiographic diagnosis. This study was therefore performed to assess the incidence of angiographic mitral valve prolapse in a group of patients unselected for their primary cardiac diagnosis. When possible, angiographic and echocardiographic findings were correlated.

Patients and Methods

Angiograms: The left ventricular cineangiograms from all patients studied at the Victoria General Hospital during a 12 month period were reviewed. Only those studies performed through a retrograde catheter, filmed in the 30° right anterior oblique projection and having satisfactory technical quality were accepted for analysis. The study group then consisted of 336 patients of whom 223 were male and 113 were female; their ages ranged from 13 to 71 years (mean 47 years).

Without prior knowledge of the clinical or hemodynamic diagnosis, at least two of us independently reviewed all angiograms. When opinion differed, a third reviewer arbitrated. End-systolic frames in the right anterior oblique projection were assessed for the presence of bulging of the posterior mitral leaflet into the left atrium.[12] If such bulging were present, the degree of prolapse was graded on a scale of 1 to 3 (mild to severe) on the basis of a subjective assessment of the volume of the leaflet bulge (Fig. 1). In addition, the number of involved scallops was tabulated according to criteria recently suggested by angiopathologic correlation.[12] Thus, a bulge inferiorly and posterior was considered due to the posteromedial commissural scallop and a bulge anterior and laterally was considered due to the anterolateral commissural scallop. A bulge superiorly along the plane of the mitral ring, usually visible posterior to the aortic root, was considered due to the medial scallop.

After completion of the angiographic analysis, the patients were grouped according to their final diagnosis. For this purpose, patients with a discharge diagnosis of mitral valve prolapse (based on angiographic appearance) were assigned to the "normal" group unless they also had clinical evidence of the click-murmur syndrome.

Echocardiograms: All available echocardiograms from this patient group were reviewed. Because the orientation of the transducer was not known with certainty, tracings were accepted for analysis only if both mitral leaflets were visible with the left atrial wall posteriorly. Of the 336 patients, 140 had echocardiograms that were of satisfactory technical quality and met these criteria. As other workers have suggested,[15,17,18] only two patterns of systolic mitral valve motion, midsystolic buckling and pansystolic posterior bowing or collapse (Fig. 2), were accepted as indicative of prolapse.

Results

Angiographic findings (Table I): Of the 131 patients with significant coronary artery disease (defined as greater than 75 percent luminal narrowing in one or more major coronary vessels), 52 (40 percent) had end-systolic bulging of at least one posterior leaflet scallop. A similar incidence rate was found in patients with congenital heart disease (42 percent) and in those with valve disease of rheumatic origin (32 percent); it was somewhat less in the small group with cardiomyopathy (16 percent) and greater in those considered normal (60 percent). The latter group consisted primarily of patients with complaints of chest pain without angiographic evidence of significant coronary artery disease. Six patients had the auscultatory features of the click-murmur syndrome and, as expected, all had angiographic evidence of mitral valve prolapse. Thus, of the 336 patients, 143 (43 percent) had angiographic end-systolic bulging of one or more posterior leaflet scallops.

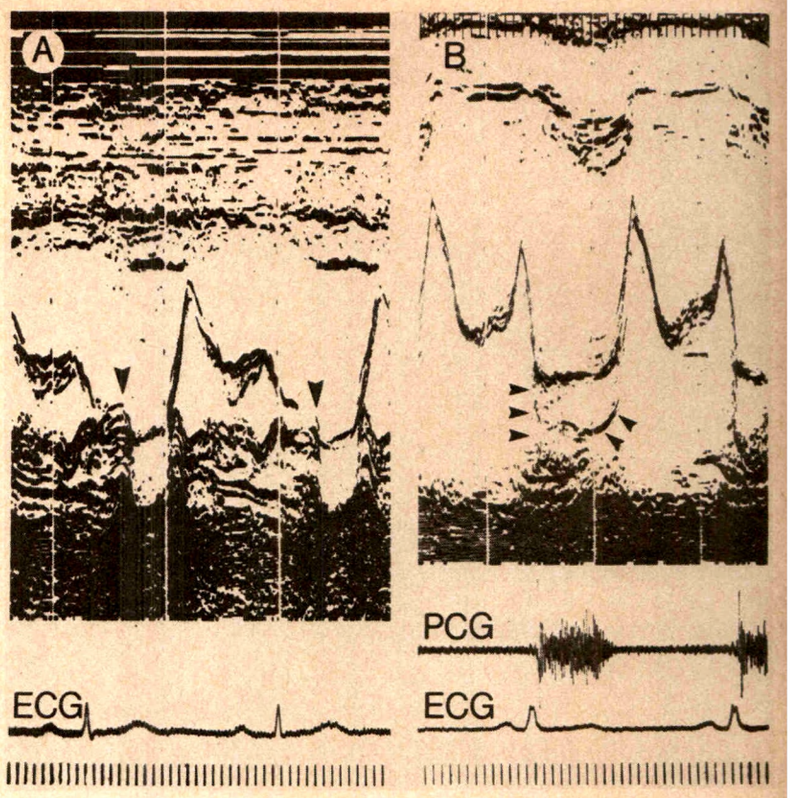


FIGURE 2. Echocardiograms illustrating the patterns of mitral valve motion accepted in this study as indicative of mitral valve prolapse. **A, arrow** indicates the abrupt mid-systolic buckling of the mitral leaflets. **B, arrows** outline the pansystolic posterior bowing of the mitral leaflets. The simultaneously recorded phonocardiogram (PCG) shows the pansystolic murmur of mitral regurgitation. ECG = electrocardiogram.

In 85 percent of the patients with angiographic prolapse (121 of 143) the severity of prolapse was qualitatively assessed as mild (grade 1); in 18 it was judged moderate (grade 2) and in only 4 was it judged severe (grade 3). In the six patients with the click-murmur syndrome, the prolapse was classified as grade 1 in one; in the remaining five patients it was judged grade 2 or grade 3.

Similarly, the majority of patients (94 of 143) had prolapse of one scallop, predominantly the posteromedial scallop. Only 6 patients had involvement of all three scallops, the remaining 43 having prolapse of two scallops. Although patients judged to have grades 2 and 3 prolapse tended to have more scallops involved, there was considerable individual variability. The presence of the auscultatory phenomena of click and murmur did not predict the number of scallops involved; patients with these findings had an equal incidence of one, two and three scallop prolapse.

Echocardiographic findings (Table II): All six patients with the click-murmur syndrome had satisfactory echocardiographic tracings and each had ultrasonic evidence of prolapse; five had mid-systolic leaflet buckling and one had pansystolic posterior bowing. Only three other patients had echocardiographic evidence of prolapse; all were studied because of chest pain and were found to have no significant coronary artery disease. Because these three patients did not

TABLE I

Angiographic Findings

Diagnosis	Total Patients (no.)	Patients With Prolapse		Severity of Prolapse (grade)			Scallops Involved (no.)		
		no.	%	1	2	3	1	2	3
Coronary artery disease	131	52	40	47	5	0	33	18	1
Normal	84	50	60	43	6	1	35	14	1
Congenital heart disease	12	5	42	4	1	0	2	2	1
Cardiomyopathy	19	3	16	3	0	0	3	0	0
Rheumatic valve disease	84	27	32	23	4	0	19	7	1
Click-murmur syndrome	6	6	100	1	2	3	2	2	2
Total	336	143	43	121	18	4	94	43	6

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TABLE II

Echocardiographic Findings

Diagnosis	Total Patients (no.)	Patients With Prolapse	
		no.	%
Coronary artery disease	26	0	0
Normal	31	3	10
Congenital heart disease*	4	0	0
Cardiomyopathy	16	0	0
Rheumatic valve disease	57	0	0
Click-murmur syndrome	6	6	100
Total	140	9	6

*All had secundum atrial septal defect.

have the clinical features of the click-murmur syndrome they were included in the normal group. Thus, of the 140 patients analyzed, only 9 (6.4 percent) had echocardiographic evidence of mitral valve prolapse.

Discussion

It is now well established that patients with the click-murmur syndrome are characterized angiographically by end-systolic bulging of one or both mitral leaflets into the left atrium with or without associated mitral regurgitation. However, as this study and others[4,19,20] have demonstrated, the same angiographic pattern also occurs in patients who have neither the auscultatory phenomena nor mitral regurgitation. A central problem relates to the clinical significance of this observation: that is, do patients with only the angiographic pattern of prolapse have an abnormal mitral apparatus and, if so, is the abnormality associated with substantial risk of endocarditis,[22] progressive mitral regurgitation[23] and sudden death,[3,24] as is believed to be the case in the auscultatory click-murmur syndrome? Our finding that so-called silent mitral valve prolapse occurred in approximately 40 percent of consecutive angiograms, without predilection for any specific diagnostic subgroup, strongly suggests that the angiographic pattern by itself cannot be considered indicative of pathologic mitral valve function.

Angiographic criteria for mitral valve prolapse: The angiographic diagnosis of mitral valve prolapse depends to a considerable degree on subjective assessment and the frequency with which it is made will vary somewhat among institutions. One might argue that many or most of the angiograms that we considered to reveal prolapse (particularly those judged grade 1 severity) were normal. Whereas we expect that this is largely true, several observations seem pertinent. First, one of our patients with the click-murmur syndrome was assessed to have grade 1 prolapse, indicating that the auscultatory abnormalities may be associated with relatively minor degrees of leaflet bulging. Second, our findings are similar to those of others. Thus, 40 percent of our patients with significant coronary artery disease had angiographic prolapse, a figure that agrees closely with the results of Aranda et al.[20] Because the majority of our patients with coronary disease (47 of 52) were judged to have grade 1 prolapse, we conclude that our criteria for angiographic diagnosis were similar to those of Aranda et al. Likewise, in our group with congenital heart disease, eight had a secundum atrial septal defect and three of these (38 percent) had angiographic mitral valve prolapse. This incidence is virtually identical to that reported by Betriu et al.[19] in a larger series. Of our three patients with a septal defect and angiographic prolapse, two were judged to have prolapse of grade 1 severity and one to have prolapse of grade 2 severity. These findings also suggest that our criteria for angiographic diagnosis were similar to those of other workers.

Although the incidence of true prolapse in our patient population is unlikely to approach the 43 percent figure suggested by our angiographic analysis, we do not know the actual number of patients with pathologic mitral valve function. For instance, it is possible that more than six patients had the click-murmur syndrome but were not evident clinically without specific provocative maneuvers.[5] Nevertheless, one would not expect to find a provocable click-murmur syndrome in 40 percent of the patient population. It is also possible that mitral valve prolapse is not a single disease entity but the common denominator of many diverse influences on the mitral valve apparatus.[25] In this case, one would expect a significant incidence of prolapse in any condition with the potential for interference with normal mitral valve function. However, this explanation does not completely account for our findings, particularly in light of the total spectrum of left ventricular size and function encompassed by the diagnostic subgroups. Thus, although our data probably underestimated the number of patients with true mitral valve prolapse, they suggest that accurate identification of such patients is not possible solely with assessment of the end-systolic configuration of the left ventricular angiogram. Improved angiographic criteria are needed; such criteria will probably require some assessment of dynamic valve function throughout the cardiac cycle in addition to the presence of end-systolic leaflet bulging. In this regard, perhaps some index of shortening of mitral valve axes, as recently suggested by Farry et al.,[26] will prove useful.

In light of our results, it is not surprising that mitral valve prolapse (diagnosed angiographically) is reported to be frequently associated with other clinical entities. However, it seems unwarranted to assume that such association indicates a pathogenetic relation. Using currently accepted angiographic criteria, one might well diagnose prolapse in patients with entirely normal mitral valve function—a particularly likely occurrence in patients with no other identifiable cardiac disease. Thus, patients with chest pain or arrhythmia and no demonstrable hemodynamic or coronary angiographic abnormality seem more likely to be considered to have mitral valve prolapse than those with a similar configuration of the end-systolic angiogram but with definite

abnormalities of the coronary vasculature, valves or myocardium. This may not only result in the "production" of disease, but also interfere with the search for other explanations for the clinical presentation of these patients.

Echocardiographic criteria for mitral valve prolapse: If, as our data suggest, the angiographic criteria for the diagnosis of prolapse are nonspecific, one must also question the echocardiographic criteria that have been proposed solely on the basis of angiographic correlation.[15,16] However, there are numerous observations[15–18] to suggest that abrupt mid-systolic buckling of the mitral leaflets (Fig. 2A) is indicative of true mitral valve prolapse. Similarly, pansystolic posterior bowing of the leaflets (Fig. 2B) is probably a reliable sign of prolapse provided adequate care has been taken to avoid excessive inferior angulation of the ultrasonic transducer.[18,27] Our retrospective study was not designed to examine echocardiographic criteria and therefore provides limited information concerning the diagnostic reliability of the ultrasonic technique. However, all patients with the click-murmur syndrome had echocardiographic evidence of mitral valve prolapse, and only three other patients had echocardiograms that might represent false positive diagnoses. Our findings therefore suggest that echocardiography may be more specific than angiography in providing objective evidence of mitral valve prolapse. However, they provide no information on the diagnostic sensitivity of the technique and it is likely that some patients with true prolapse had no echocardiographic abnormality.[17,18]

Auscultatory criteria for mitral valve prolapse: Central to any discussion of mitral valve prolapse is its prevalence in the population. Although prolapse was initially considered an uncommon disorder, recent studies[17,18] suggest that it affects perhaps as many as 6 to 17 percent of "normal" young women, at least as reflected by the presence of a systolic click or murmur, or both. If these auscultatory signs are always indicative of mitral valve disease, then the incidence of complications of the disorder, such as sudden death and endocarditis, must be extremely small. However, although it seems likely that a significant derangement of mitral valve function is indicated by a click followed by a late systolic crescendo murmur, the same may not be true for clicks alone or for murmurs that end before the second heart sound. Thus, some systolic clicks may arise from sources other than the mitral valve and, on occasion, may be extracardiac in origin, as earlier workers have suggested.[28] The finding that patients with an isolated click often have bulging posterior leaflet scallops on angiography does not, in our opinion, prove that they have an abnormal mitral valve.

Clinical implications: Although mitral valve prolapse may be associated with any of several serious complications, no totally satisfactory standard for diagnosis is available. Our results indicate that some end-systolic bulging of one or more scallops of the posterior mitral leaflet is a common angiographic finding that almost certainly does not reflect mitral valve disease in many cases. We therefore suggest that the angiographic diagnosis of mitral prolapse be made with caution in the absence of other signs of the syndrome. Obviously there is an urgent need for careful prospective clinical, echocardiographic, angiographic and pathologic studies in patients with the click-murmur syndrome; the goal of such studies must be to provide reliable criteria for the diagnosis of significant valve prolapse so that patients at risk of serious complication can be identified and appropriately managed.

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Short- and Long-Term Effects of Digitalis on Resting and Posthandgrip Hemodynamics in Patients With Coronary Artery Disease

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The short-term effects at rest of 0.01 mg/kg of ouabain given intravenously and the long-term effects at rest of daily oral administration of 0.25 mg of digoxin on left ventricular ejection fraction, left ventricular end-diastolic volume, cardiac index, blood pressure and heart rate were measured in eight patients with coronary artery disease using a single crystal scintillation probe. Measurements were also made after handgrip exercise (1 minute of 33 percent of maximal) in two of these patients and in two others with coronary artery disease. In all patients the left ventricular ejection fraction was less than 0.50. Ouabain increased resting left ventricular ejection fraction (0.39 ± 0.03 to 0.55 ± 0.03 [mean ± standard error of the mean], $P < 0.01$) and decreased resting left ventricular end-diastolic volume index (86 ± 12 to 64 ± 5 ml/m^2, $P < 0.01$) and heart rate (75 ± 6 to 69 ± 6 beats/min, $P < 0.02$). Ouabain did not change resting cardiac index or blood pressure significantly. Handgrip exercise increased heart rate and blood pressure significantly. Left ventricular ejection fraction after handgrip exercise was 0.33 ± 0.02 (difference not significant), but it increased after ouabain administration to 0.55 ± 0.03 from the control value of 0.36 ± 0.01 ($P < 0.05$). After 2 weeks of daily oral administration of digoxin, associated with a digoxin level of 1.0 ± 0.2 ng/ml, all resting hemodynamic variables were statistically unchanged from control levels. In the four patients tested daily, the return to control levels took 1 to 5 days. Left ventricular ejection fraction after handgrip exercise remained elevated at 0.50 ± 0.04 ($P < 0.05$). Thus, with long-term digoxin administration, volumetric variables at rest are initially improved but later return to control values whereas values after exercise continue improved.

Digitalis preparations have been widely recommended for the treatment of congestive heart failure[1–7] including that caused by coronary artery disease.[8–10] Studies measuring the short-term hemodynamic effects of digitalis have shown both improvement in cardiac contractility[11–14] and decrease of right and left ventricular filling pressures.[15–18] Cardiac output, however, has frequently been shown not to increase.[13,17–23] Recent work from our institution[24] has demonstrated a short-term increase in the left ventricular ejection fraction after administration of ouabain in patients with coronary artery disease. This finding provides further evidence of the primary cardiac effects of digitalis previously documented with the use of isovolumic phase contractility variables.[13,14,21,22]

Few data exist to document the continued effect of digitalis on hemodynamics in patients with coronary artery disease. Directly measured changes in hemodynamic variables in normal persons have been shown to disappear in approximately 5 days.[25,26] Data on indirect measurements (systolic time intervals) in long-term studies have been conflicting[27–29] although persistent directly measured inotropic changes have been demonstrated in experimental animals.[30] We undertook this study to confirm the short-term hemodynamic changes of digitalization and

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to determine whether these changes persist in patients with coronary artery disease and left ventricular dysfunction.

Methods

Patients

Ten men (Cases 1 to 10) aged 46 to 61 years, were informed of the nature of the study and consented to participate. Patients 1 to 8 underwent measurements at rest, and Patients 2, 4, 9 and 10 underwent measurements both at rest and after exercise. Patients 1 and 6 had isolated left anterior descending coronary arterial obstruction (greater than 70 percent of luminal diameter), Patients 7 had two vessel coronary artery disease and the remaining seven patients had three vessel disease. Left ventricular ejection fraction ranged from 0.20 to 0.45 as assessed from single plane angiographic films in the right anterior oblique projection obtained at prior cardiac catheterizations. Patients 5 and 7 had no angina; the remaining eight patients had one to six episodes of angina daily. Patients 2, 4, 8 and 9 required diuretic drugs for clinical congestive heart failure. Patient 6 had an occluded single left anterior descending coronary bypass graft, Patient 8 had occluded left anterior descending and right coronary bypass grafts; the remaining eight had had no operative intervention. All patients had normal sinus rhythm and none had valvular heart disease.

TABLE I

Hemodynamic Data at Rest After Ouabain and After 2 Weeks of Maintenance Digoxin in Eight Patients With Coronary Artery Disease (Group 1)

Case no.	BP	HR	CI	EF	SVI	EDVI
1						
Control	134/86	60	2.8	0.40	46	116
Ouabain	152/88	48	1.9	0.50	41	81
Digoxin	126/88	64	2.6	0.73	40	55
2						
Control	120/100	68	3.0	0.35	44	126
Ouabain	122/92	64	2.3	0.42	36	86
Digoxin	108/76	68	2.2	0.32	32	99
3						
Control	116/74	84	2.6	0.47	31	66
Ouabain	118/72	72	2.4	0.63	33	53
Digoxin	110/80	76	2.7	0.42	35	84
4						
Control	110/86	75	2.1	0.36	29	79
Ouabain	106/74	71	2.2	0.61	32	52
Digoxin	95/65	72	2.9	0.41	40	97
5						
Control	90/60	64	3.2	0.40	50	125
Ouabain	105/60	64	2.9	0.64	45	71
Digoxin	116/68	60	3.0	0.34	50	147
6						
Control	124/88	60	1.4	0.48	23	47
Ouabain	122/84	52	1.9	0.66	36	54
Digoxin	128/88	80	2.2	0.35	28	79
7						
Control	122/78	88	2.0	0.46	23	49
Ouabain	118/78	80	1.9	0.50	24	49
Digoxin	110/68	80	1.9	0.36	24	66
8						
Control	122/82	104	1.9	0.24	18	76
Ouabain	142/92	100	2.1	0.45	20	47
Digoxin	128/92	100	2.1	0.34	21	62

BP = blood pressure (mm Hg); CI = cardiac index (liters/min per m^2); EDVI = left ventricular end-diastolic volume index (ml/m^2); EF = left ventricular ejection fraction; HR = heart rate (beats/min); SVI = stroke volume index (ml/m^2).

Protocol

Hemodynamic testing: Patients stopped taking digitalis and propranolol 2 weeks and 2 days, respectively, before testing. Isosorbide dinitrate and nitroglycerin were not administered within 6 hours of hemodynamic testing. Left ventricular ejection fraction, cardiac index, stroke volume index and left ventricular end-diastolic volume index were determined with use of the single 2 inch (5.1 cm) crystal scintillation probe technique with background correction as described by Van Dyke and Steele and their co-workers.[31,32] The center of the left ventricular silhouette was fluoroscopically determined and an initial 1 mCi dose of indium-113m was used for the left ventricular curve and 0.5 mCi for the background curve. The indium was injected into the superior vena cava through a catheter introduced percutaneously into either the external jugular vein or a brachial vein. The left ventricular ejection fraction was calculated as the ratio of the difference between the systolic and diastolic count rates divided by the diastolic count rate, with background counts subtracted from the systolic and diastolic values. Cardiac index was determined with use of the area under, and equilibration value of, the left ventricular curve.[33] Stroke volume index was defined as cardiac index divided by heart rate, and left ventricular end-diastolic volume index as stroke volume index divided by left ventricular ejection fraction. Blood pressure was determined with a sphygmomanometer.

Ouabain: The control hemodynamic variables obtained at rest were measured during and after 15 minutes of supine rest in the eight patients in group 1 studied only at rest (Cases 1 to 8). In subsequent studies, four patients (Cases 2, 4, 9 and 10) additionally had repeat testing while performing 33 per-

TABLE II

Hemodynamic Data at Rest and After Handgrip Exercise in the Control State, After Ouabain and After 2 Weeks of Maintenance Digoxin in Four Patients With Coronary Artery Disease (Group 2)

Case no.	BP	HR	CI	EF	SVI	EDVI
2						
Control, R	108/74	60	2.1	0.39	35	90
Control, H	130/100	65	2.3	0.33	51	154
Ouabain, R	114/78	55	1.7	0.42	31	74
Ouabain, H	135/100	60	1.6	0.50	27	53
Digoxin, R	116/84	60	1.7	0.51	28	56
Digoxin, H	122/92	60	2.0	0.56	33	60
4						
Control, R	110/82	60	1.8	0.37	30	81
Control, H	132/106	80	2.0	0.35	25	71
Ouabain, R	118/92	55	1.2	0.50	22	44
Ouabain, H	146/112	70	1.6	0.68	23	34
Digoxin, R	110/76	60	1.8	0.34	30	88
Digoxin, H	118/90	80	1.6	0.38	20	53
9						
Control, R	93/60	70	2.9	0.35	41	118
Control, H	112/80	80	2.4	0.36	30	83
Ouabain, R	90/60	60	2.2	0.46	37	80
Ouabain, H	120/80	75	2.3	0.54	31	57
Digoxin, R	106/68	65	2.5	0.35	38	110
Digoxin, H	120/80	75	3.2	0.54	43	79
10						
Control, R	130/78	65	2.0	0.33	31	93
Control, H	144/94	70	1.7	0.27	24	90
Ouabain, R	128/76	70	1.8	0.34	26	76
Ouabain, H	144/94	70	1.7	0.47	24	52
Digoxin, R	118/77	70	2.8	0.32	40	125
Digoxin, H	130/84	75	2.6	0.53	35	65

H = after handgrip exercise; R = at rest. Other abbreviations as in Table I.

TABLE III

Hemodynamic Measurements at Rest (average ± standard error of the mean) in the Control State, After Ouabain and After 2 Weeks of Maintenance Digoxin in Eight Men With Coronary Artery Disease (Group 1)

	EF	CI	SVI	EDVI	HR	BP
Control	0.39	2.4	33	86	75	117/82
	± 0.027	± 0.22	± 4.3	± 12	± 5.5	± 4.6/4.1
Ouabain	0.55	2.2	33	64	69	123/80
	± 0.034	± 0.12	± 2.8	± 5.4	± 5.8	± 5.8/3.9
	$P < 0.01$*	NS†	NS	$P < 0.01$	$P < 0.02$	NS/NS
Digoxin	0.41	2.5	35	90	75	115/78
	± 0.047	± 0.14	± 3.3	± 11	± 4.4	± 4.1/3.7
	NS	NS	NS	NS	NS	NS/NS

*Compared with control values.
†Not statistically significant.
NS = not significant; P = probability; other abbreviations as in Table I.

cent of maximal handgrip maneuver initiated 1 minute before testing. Handgrip exercise was performed by squeezing a sphygmomanometer bulb and was measured with the sphygmomanometer. Then 0.01 mg/kg of ouabain was administered intravenously over a period of 15 minutes under electrocardiographic monitoring. After an additional period of 15 minutes, all variables were redetermined at rest and after handgrip exercise for those so previously tested.

Digoxin: The patients were then given daily oral doses of 0.25 mg of digoxin. At the end of 2 weeks, a serum digoxin level was drawn approximately 5 hours after the daily digoxin dose and all hemodynamic variables were again measured during and after 15 minutes of supine rest, with repeat handgrip testing additionally for the four patients who had previously been so tested. Four of the eight patients in the first group (Cases 1, 2, 4 and 8) were tested a second time at rest, after ouabain administration, and daily thereafter for 5 days while continuing to receive the daily dose of digoxin. Serum digoxin levels were assayed by the Kallestad Laboratories, Inc ^{125}I-Digoxin Quantitope® technique.

Statistical change of the means of the hemodynamic variables was determined using Student's paired t test.

TABLE IV

Hemodynamic Data (average ± standard error of the mean) in Four Patients (Cases 2, 4, 9 and 10) Before and After Ouabain and After 2 Weeks of Maintenance Digoxin

	Ejection Fraction	Cardiac Index (liters/min per m^2)	Heart Rate (beats/min)	Blood Pressure (mm Hg)
Control				
Rest	0.36 ± 0.01	2.2 ± 0.2	64 ± 2	110/74 ± 8/5
Handgrip	0.33 ± 0.02	2.1 ± 0.2	74 ± 4	131/95 ± 7/6
	NS*	NS		
After Ouabain				
Rest	0.41 ± 0.04	1.7 ± 0.2	60 ± 4	113/77 ± 8/7
	NS	$P < 0.02$		
Handgrip	0.55 ± 0.05	1.8 ± 0.2	69 ± 3	136/97 ± 6/7
	$P < 0.05$†	$P < 0.05$		
After digoxin				
Rest	0.38 ± 0.04	2.2 ± 0.3	64 ± 2	113/77 ± 3/3
	NS	NS		
Handgrip	0.50 ± 0.04	2.4 ± 0.4	73 ± 4	122/87 ± 3/3
	$P < 0.05$	NS		

*Not statistically significant.
†Compared with control value at rest.

Results

Resting hemodynamics: Individual patient hemodynamic data in group 1 (Cases 1 to 8), who underwent resting measurements, and in group 2 (Cases 2, 4, 9 and 10), who underwent resting and posthandgrip measurements, are shown in Tables I and II, respectively. The mean values for the resting hemodynamic variables measured in the eight patients in group 1 are shown in Table III. The mean resting cardiac index of 2.4 liters/min per m^2 is consistent with mild congestive heart failure for the group as a whole. Left ventricular ejection fraction increased and heart rate and left ventricular end-diastolic volume index were significantly decreased from mean control values after administration of ouabain. The other measured variables did not change significantly. After 2 weeks of digoxin administration, all values were statistically unchanged from control levels. The mean serum digoxin level at this time was 1.0 ± 0.2 ng/ml (average ± standard error of the mean). Individual patient values for left ventricular ejection fraction, cardiac index and left ventricular end-diastolic volume index are shown in Figures 1 to 3.

In all four patients who underwent additional daily hemodynamic measuring (Cases 1, 2, 4 and 8), left ventricular ejection fraction returned to, or dropped below, control level on the first, second, fifth and third day, respectively, after digitalization (Fig. 4).

Posthandgrip hemodynamics: The mean resting and posthandgrip hemodynamic measurements in group 2 are shown in Table IV. In Patients 2 and 4 resting left ventricular ejection fraction was similar to that previously determined but blood pressure and cardiac index showed some variation. Resting left ventricular ejection fraction for all four patients increased, but not significantly, after ouabain administration. After 2 weeks, ejection fraction was again not significantly different from control levels. Resting cardiac index decreased significantly with short-term digitalization, but was unchanged from control levels after 2 weeks.

Handgrip exercise resulted in an overall mean increase in blood pressure from 112/76 ± 4/3 to 130/93 ± 3/3 mm Hg ($P < 0.01$) and in heart rate from 63 ± 2 to

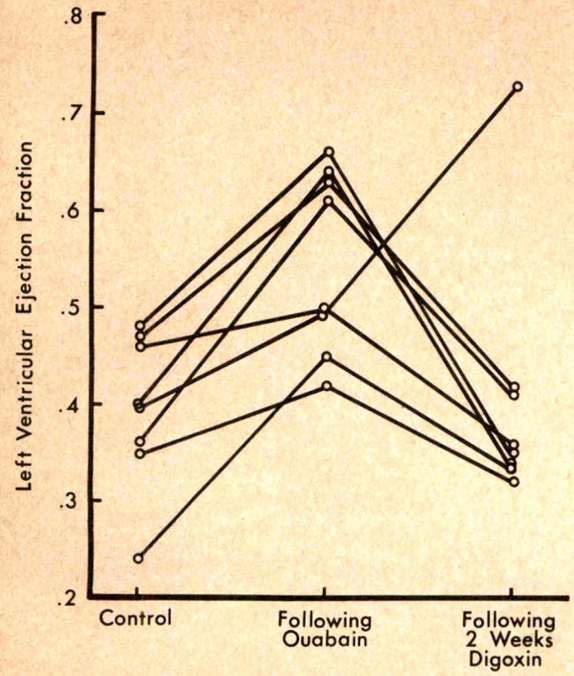


FIGURE 1. Left ventricular ejection fraction at rest before and after 0.01 mg/kg of ouabain intravenously, and after 2 weeks of daily oral administration of 0.25 mg of digoxin in eight patients with coronary artery disease (Cases 1 to 8, group 1).

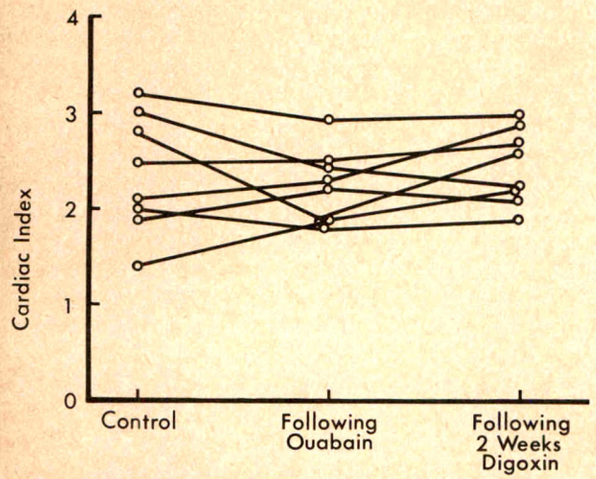


FIGURE 2. Cardiac index (liters/min per m^2 at rest before and after 0.01 mg/kg of ouabain intravenously and after 2 weeks of daily oral administration of 0.25 mg digoxin in eight patients with coronary artery disease (Cases 1 to 8, group 1).

72 ± 2 beats/min ($P < 0.05$) for the control, postouabain and 2 week digoxin studies combined. Posthandgrip left ventricular ejection fraction decreased nonsignificantly before digitalis but was significantly higher than control level both after digitalization and after 2 weeks of maintenance digoxin therapy. Cardiac index dropped from control levels with handgrip exercise after digitalization and was nonsignificantly higher than control level after 2 weeks of maintenance therapy.

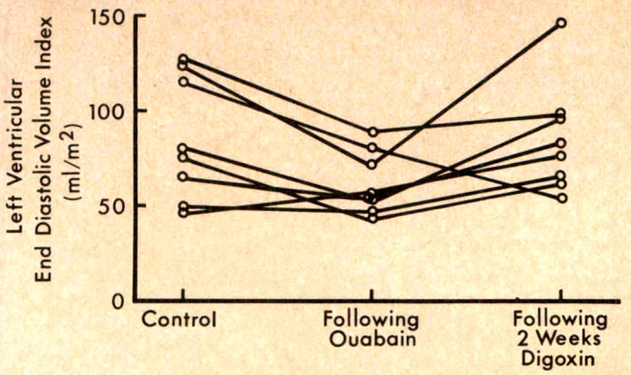


FIGURE 3. Left ventricular end-diastolic volume index at rest before and after 0.01 mg/kg of ouabain intravenously and after 2 weeks of daily oral administration of 0.25 mg of digoxin in eight patients with coronary artery disease (Cases 1 to 8, group 1).

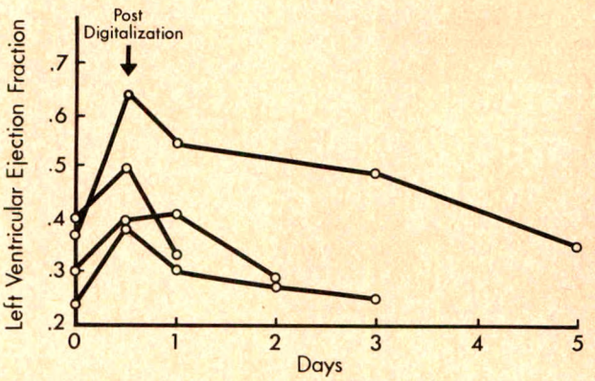


FIGURE 4. Left ventricular ejection fraction at rest before and after 0.01 mg/kg of ouabain intravenously and daily in four patients with coronary artery disease (Cases 1, 2, 4 and 8, group 1).

Discussion

Validity of single crystal scintillation probe method: Although not widely used, the single crystal scintillation probe method using background correction has been shown to have good correlation with standard techniques. Berndt et al.[34] and Steele et al.[32] both found a correlation coefficient of 0.90 between left ventricular ejection fraction measured with angiography and the scintillation probe method in groups of 17 and 36 patients, respectively, with left ventricular ejection fractions ranging from 0.10 to 0.85 and 0.18 to 0.90, respectively. Berndt et al.[34] also found a 0.88 correlation coefficient between cardiac output measured with the dye-dilution or Fick method and scintillation probe method as well as the same good correlation between left ventricular end-diastolic volume index measured with angiography and scintillation probe method in patients without valve insufficiency.

Short-term digitalization with ouabain: This procedure resulted in a small decrease in heart rate and a statistically insignificant increase in blood pressure similar to that reported by Murphy et al.[3] The statistically insignificant short-term change in cardiac index

agrees with the findings of several investigators[13,18,19,23] whose patient populations had various degrees of left ventricular dysfunction. Others[21,22,35] also found no improvement in cardiac output, although their studies were in the setting of acute myocardial infarction. In contrast, Ferrer et al.[9] showed an increase in cardiac output in patients with class IV congestive failure, and Bloomfield et al.[8] demonstrated a similar effect although 4 of 10 patients in their study had atrial fibrillation.

As previously reported from our institution[24] and in contrast to the data of De Mots et al.[18] mean left ventricular ejection fraction increased acutely by 41 percent. This increase was associated with a decreased left ventricular end-diastolic volume index and an unchanged stroke volume index. We believe that this represents, in part, a primary increase in cardiac contractility because afterload did not statistically change and left ventricular ejection fraction is largely insensitive to changes in preload.[36] Recent work[37] has shown closer correlation of clinical congestive heart failure with contractility indexes of the ejection rather than of the isovolumic phase. Our findings support the previously reported evidence for an increase in contractility after acute digitalis administration as assessed with isovolumic phase indexes.[11–14]

Although left ventricular end-diastolic pressure was not measured, there was a 26 percent decrease in left ventricular end-diastolic volume index, and a reduction in this variable is thought to correlate with a decrease in end-diastolic pressure. Such a decrease in end-diastolic volume index has been shown by others.[3,18,22,23] A part of this decrease may represent peripheral pooling effects of digitalis.[15,16]

Long-term effects of digoxin: Resting hemodynamic variables returned to predigitalization levels by the end of 2 weeks despite initially significant changes in heart rate, left ventricular end-diastolic volume index and left ventricular ejection fraction. Only one of the eight patients (Case 1) had a persistent increase in left ventricular ejection fraction (0.73) after 2 weeks. On subsequent restudy 5 months after the initial digitalization he had a left ventricular ejection fraction of 0.44 compared with an initial value of 0.40 despite continued maintenance digitalis therapy. The small possibly significant transient decrease in cardiac index with short-term digitalization is in accord with the findings of Rytand[25] and Rodman et al.,[26] who demonstrated disappearance of the decrease in cardiac output and venous pressure in 3 to 7 days in normal persons receiving maintenance doses of digitalis. The mean serum digoxin level of 1.0 ng/ml for the group (range 0.4 to 1.8 ng/ml) suggests patient compliance with a regimen of 0.25 mg of digoxin daily.[38]

In contrast to the lack of sustained resting hemodynamic improvement, the increase in posthandgrip left ventricular ejection fraction was almost as great after 2 weeks of maintenance therapy as immediately after digitalization. The short-term improvement confirms the findings of Murphy et al.,[3] who found improved hemodynamics with exercise after digitalization. It is also in agreement with the long-term effects of digitalis in normal dogs reported by Mahler et al.,[30] who found a more significant change in left ventricular wall motion over time with an increased afterload. Also in agreement with the latter study is our finding of unchanged left ventricular volume after 2 weeks of digitalis.

Hoeschen and Cuddy[28] and Carliner et al.[29] did find persistent systolic time interval changes at rest with long-term digitalis administration, although Davidson and Gibson[27] did not. A possible explanation for such a persistent effect at rest is that systolic time interval measurements reflect changes in rate of rise of left ventricular pressure more than changes in volumetric indexes such as left ventricular ejection fraction. A persistent increase in the rate of change of left ventricular pressure was demonstrated by Carliner et al.[29]

In summary, our study suggests that short-term digitalis administration improves both resting and exercise volumetric indexes of contractility (left ventricular end-diastolic volume index, left ventricular ejection fraction) in patients with coronary artery disease, whereas only exercise volumetric indexes are improved with long-term administration. Resting volumetric hemodynamics return to predigitalization levels in a few days in patients with clinically mild congestive heart failure.

Acknowledgment

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Effect of Lidocaine on Escape Rate in Patients With Complete Atrioventricular Block

A. Distal His Bundle Block

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Lidocaine was administered intravenously as a 1.5 mg/kg bolus injection followed by a 2 to 4 mg/min infusion to 18 patients with complete atrioventricular (A-V) block to determine its safety in this situation. As an electrophysiologic corollary, the in vivo effects of lidocaine on ventricular automaticity in man were also evaluated. In 13 of the 18 patients, the ventricular rate was either unchanged or slowed by 16 percent or less after administration of lidocaine. In the remaining five patients, the rate slowed abruptly in a manner suggesting 2:1 or 3:1 exit block. The site of block was located distal to the His bundle potential in these five patients and in eight others who did not exhibit exit block. It is concluded that (1) the pacemaker fibers responsible for the ventricular escape rhythm were insensitive to the effects of lidocaine, thereby suggesting that the spontaneous depolarization in those fibers may be slow channel-dependent; (2) lidocaine is nonetheless unsafe to use in patients with complete A-V block located distal to the His bundle potential without prior pacemaker insertion because of the risk of inducing high grade exit block; (3) the development of exit block depends more on a critical degree of His-Purkinje conduction abnormality than on the rate of lidocaine administration or the plasma drug level achieved; and (4) patients at risk for the development of exit block cannot be identified on the basis of clinical presentation.

This study was designed to assess the effects of lidocaine on the ventricular escape rate in patients with complete atrioventricular (A-V) block. Our reasons for performing the study were twofold: (1) Recent reports regarding the safety of lidocaine in such patients require clarification, and (2) the ventricular escape rhythm that occurs in such patients is one of the few clinical examples of an ectopic rhythm that can be ascribed with certainty to automaticity. As such, it offers the opportunity to determine the effects of lidocaine on this electrophysiologic variable in man.

The confusion regarding the safety of lidocaine in these patients has arisen from observations showing that lidocaine caused no slowing of the rate of the ventricular escape rhythm in five patients with complete A-V block,[1] although it suppresses spontaneous diastolic depolarization in Purkinje fibers,[2,3] slows the rate of the ventricular escape rhythm in dogs with surgically induced complete A-V block,[4] may cause marked delay in the reestablishment of the autonomous ventricular rhythm after cessation of ventricular pacing[5] and may induce complete A-V block in patients with preexisting intraventricular conduction disturbances.[1,5–8] We hoped that our study would resolve these seemingly incompatible observations and at the same time contribute to a better understanding of the mechanism of lidocaine's antiarrhythmic effects in man.

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Materials and Methods

Eight men and 10 women with complete atrioventricular (A-V) block and stable escape rhythm were studied after giving informed consent. All required permanent ventricular pacing. The pertinent clinical features and electrocardiographic findings are shown in Table I. Eight patients had no known heart disease before the complete block developed. Nine patients had hypertension, one had a prior myocardial infarction and four had chest pain that was not typical of angina pectoris. None of the 18 patients had had acute heart failure or liver dysfunction. Two patients had received digoxin within 3 days of the study. Although the A-V block was probably not due to digitalis because digoxin blood levels were less than 1 ng/ml, we could not rule out digitalis toxicity as a possible cause of block.

In all patients, a bipolar or tripolar pacing catheter was placed in the right ventricle before lidocaine was administered. In 13 patients, a His bundle electrogram was recorded at a frequency of 40 to 500 hertz on photographic paper moving at a speed of 100 mm/sec (Honeywell model no. 1912 Visicorder) before the pacing catheter was placed in the right ventricular apex. The electrocardiogram was continuously monitored during the entire study and was recorded using single or multiple leads at paper speeds of 25 and 50 mm/sec. Before administration of lidocaine, we recorded the electrocardiogram for 60 seconds every 2 to 5 minutes for a 30 minute period. Lidocaine was administered intravenously as a 1.5 mg/kg bolus injection given over a 2 minute period and followed immediately by an infusion of 2 to 4 mg/min for 15 to 30 minutes. The electrocardiogram was recorded continuously from the time of the lidocaine bolus dose until the R-R interval had returned to approximately the control value, and for 60 seconds every 2 to 5 minutes until at least 15 minutes after the end of the lidocaine infusion. The control R-R interval was determined by averaging all R-R intervals recorded before

TABLE I
Summary of Cases

Case no.	Age (yr) & Sex	Clinical Diagnosis	ECG	His Electrogram	Escape Rate (beat/min)*		
					Before Lidocaine	After Lidocaine	% Change After Lidocaine
			Group I (no change or gradual slowing of escape rate)				
1	67F	CHB, hyp	Sinus rhythm, QRS 0.12 second, RBBB + LAD	Distal block	41	41	0
2	76F	CHB	Sinus rhythm, QRS 0.14 second, RBBB + LAD	Distal block	40	40	0
3	74F	CHB, hyp, chest pain	Sinus rhythm, QRS 0.12 second, RBBB	Distal block	40	40	0
4	60F	CHB, hyp, chest pain	Atrial fib, QRS 0.10 second, IRBBB	Distal block	43	42	−2
5	73M	CHB	Sinus rhythm, QRS 0.14 second, LBBB + LAD	. . .	38	36	−5
6	81M	CHB, orthostatic hypotension	Atrial fib, QRS 0.10 second	Distal block	51	48	−6
7	81M	CHB	Sinus rhythm, QRS 0.08 second, LVH	. . .	33	31	−6
8	73F	CHB	Sinus rhythm, QRS 0.12 second	. . .	46	43	−7
9	72M	CHB, hyp, chest pain	Sinus rhythm, QRS 0.12 second	. . .	58	53	−9
10	78F	CHB, hyp	Sinus rhythm, QRS 0.08 second, LAD	Distal block	42	38	−10
11	74F	CHB	Sinus rhythm, QRS 0.12 second	Distal block	46	40	−13
12	71M	CHB, CAD with MI in past, hyp	Sinus rhythm, QRS 0.13 second, RBBB	. . .	40	34	−15
13	81M	CHB, hyp	Sinus rhythm, QRS 0.14 second, RBBB + LAD	Distal block	32	27	−16
			Group II (sudden slowing of escape rate)				
14	78F	CHB, hyp, chest pain	Sinus rhythm, QRS 0.08 second	Distal block	44	. . .	. . .
15	72F	CHB, hyp, pericarditis in past	Sinus rhythm, QRS 0.08 second	Distal block	32	. . .	. . .
16	69M	CHB	Sinus rhythm, QRS 0.14 second, RBBB + LAD	Distal block	31	. . .	. . .
17	78M	CHB	Sinus rhythm, QRS 0.12 second, RBBB + LAD	Distal block	33	. . .	. . .
18	46F	CHB	Sinus rhythm, QRS 0.14 second	Distal block	40	. . .	. . .

*For effects after lidocaine in Group II, see text.

CAD = coronary artery disease; CHB = complete heart block; ECG = electrocardiogram; fib = fibrillation; hyp = hypertension; IRBBB = incomplete right bundle branch block; LAD = left axis deviation; LVH = left ventricular hypertrophy; MI = myocardial infarction; RBBB = right bundle branch block.

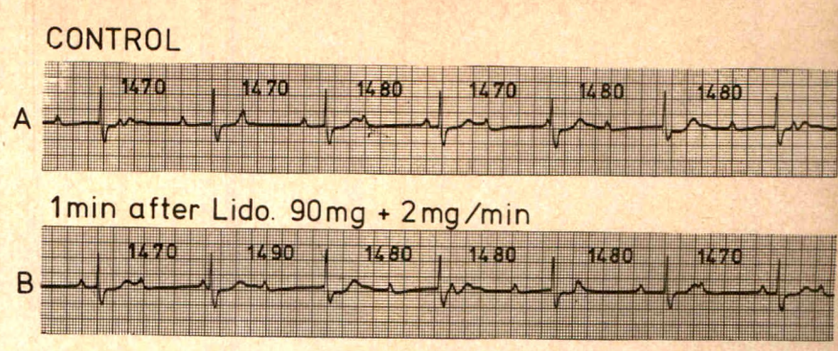


FIGURE 1. Case 3. Rhythm strips before (**control**) (**A**) and 1 minute after administration of lidocaine (Lido.) (**B,** a bolus dose of 90 mg followed by infusion at a rate of 2 mg/min). The numbers on the strips indicate R-R intervals in milliseconds. Paper speed is 25 mm/sec.

administration of lidocaine. The method of determining the maximal effect of lidocaine is presented in the Results. In eight patients, blood samples were obtained for lidocaine determinations within 1 to 5 minutes of the bolus injection. The lidocaine levels were determined with the gas-liquid chromatography method in the Department of Pharmacology, University of California, San Francisco, California. Blood pressure was monitored and the patients were observed throughout the study.

Results

The site of A-V block was distal to the location at which the His potential was recorded in all 13 patients whose His bundle electrograms were recorded. In 5 of these 13 patients, the duration of QRS complex was 0.08 to 0.10 second (narrow QRS) and in 8, it was greater than 0.10 second (wide QRS). In the five patients who did not have His bundle electrograms recorded, the QRS complex was narrow in one and wide in four. The A-H interval was normal in the 11 patients with sinus rhythm whose His bundle potentials were recorded.

Effect of lidocaine on the rate of the ventricular escape pacemaker (Table I): We have classified the patients into two groups according to the effect of lidocaine on the rate of escape rhythm. Group I consisted of 13 patients who exhibited either no change in rate of escape rhythm or gradual slowing of less than 16 percent of the control rate. Group II consisted of five patients who exhibited sudden and marked slowing in the rate of escape rhythm.

Group I (*Table I*): There were six men and seven women, aged 60 to 81 years (mean 74). The rate of escape rhythm before infusion of lidocaine ranged from 32 to 58 beats/min (mean 42). The QRS complex was wide in nine patients and narrow in four. His bundle electrograms were recorded in three of the four patients with narrow QRS complexes, and the block was located distal to the His potential in all three. We determined the maximal effect of lidocaine in these 13 patients by averaging 10 consecutive R-R intervals when the increase in R-R intervals was maximal. Lidocaine caused no change in the rate of the escape rhythm in three patients, a 2 to 7 percent decrease in rate in five patients and a 9 to 16 percent decrease in rate in five patients. The average decrease in the 13 patients was 7 ± 5 percent (standard error of the mean). In the patients whose rate of escape rhythm decreased, the maximal decrease occurred during or within 3 minutes of the bolus injection and lasted for less than 5 minutes.

Figure 1 illustrates a case in which no change in rate occurred (Case 3). The control electrocardiogram showed complete A-V block with a stable ventricular rate of 40 beats/min. The QRS complex was wide and exhibited the pattern of right bundle branch block (panel A). The His bundle electrogram showed the block distal to the His potential. The rate of escape rhythm did not change after administration of a 90 mg bolus injection followed by a 2 mg/min infusion of lidocaine (panel B). Figure 2 illustrates another example (Case 13). The QRS complex was wide with left axis deviation. The ventricular rate was 32 beats/min (panel A). The His bundle electrogram showed block distal to the His potential. The patient received a 115 mg lidocaine bolus dose followed by an infusion of 2 mg/min. A maximal decrease in the rate of escape rhythm of 16 percent occurred 1 minute after the bolus injection (panel B).

Group II (*Table I*): Two men and three women, aged 46 to 78 years (mean 68), constituted Group II. The QRS

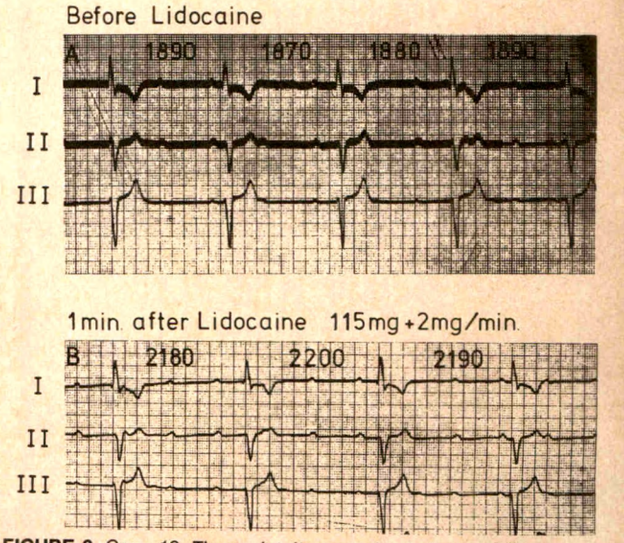


FIGURE 2. Case 13. Three simultaneous leads (I, II and III) recorded before (**control**) (**A**) and 1 minute after administration of lidocaine (**B,** a bolus dose of 115 mg followed by infusion at a rate of 2 mg/min). The numbers indicate R-R intervals in milliseconds. Paper speed is 25 mm/sec.

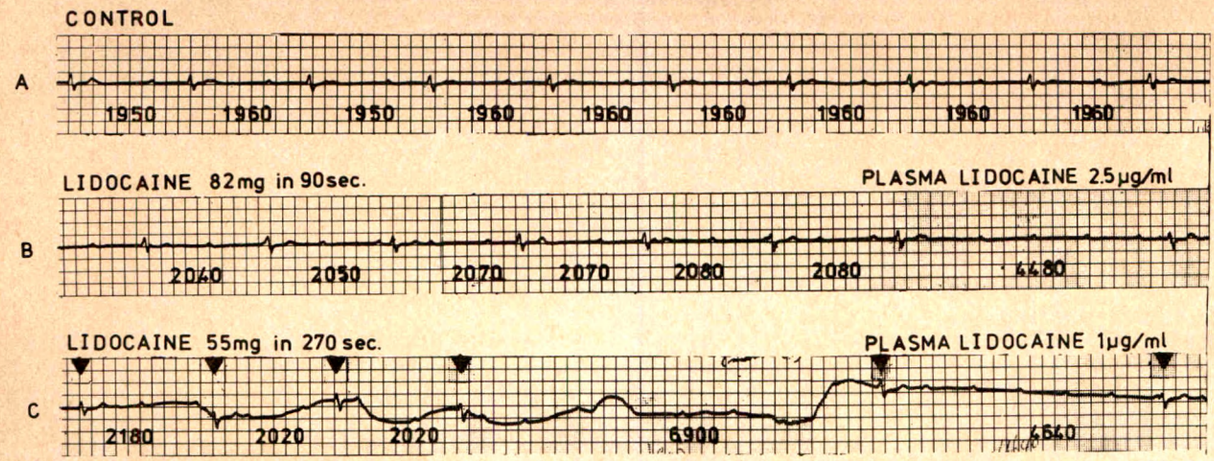


FIGURE 3. Case 16. Rhythm strips before (**control**) (**A**) and immediately after the administration of lidocaine (**B,** a bolus dose of 82 mg in 90 seconds, and **C,** an infusion of 55 mg in 270 seconds, that is, 12 mg/min for 4 minutes, 30 seconds). The numbers indicate R-R intervals in milliseconds. Paper speed is 25 mm/sec. The QRS complexes in panel **C** are marked by **closed triangles**.

complex was wide in three patients and narrow in two (both with block distal to the His potential). The rate of the escape rhythm ranged from 31 to 44 beats/min (mean 36). In three of these five patients (Cases 14 to 16) the R-R interval abruptly increased to approximately two or three times the length of the immediately preceding R-R interval. This change occurred during or within 2 minutes of the lidocaine bolus injection.

Figure 3 illustrates one of these cases (Case 16). The control electrocardiogram disclosed complete A-V block with a stable ventricular escape rhythm at a rate of 31 beats/min (panel A). The QRS complex was wide and exhibited the pattern of right bundle branch block with left axis deviation. The His bundle electrogram showed the block located distal to the His potential. During the bolus injection, the R-R interval gradually prolonged by 6 percent, as in the patients in Group I. This prolongation was followed by a sudden increase in the R-R interval to approximately two times the preceding length of the R-R interval (panel B). The lidocaine injection was discontinued and the total administered dose was calculated to be 82 mg. The plasma lidocaine level, obtained 2 minutes later, was 2.5 μg/ml. Thirty minutes later, lidocaine was readministered at a rate of 12 mg/min to determine if the slower rate of administration might be better tolerated. By 4.5 minutes after initiation of this infusion (total administered dose 55 mg), a sudden increase in the R-R interval occurred (panel C). The R-R intervals between the fourth and fifth and between the fifth and sixth QRS complexes are approximately three and two times, respectively, the length of the preceding R-R interval. The plasma lidocaine level obtained 2 minutes later was 1 μg/ml. In a fourth patient (Case 17), administration of lidocaine was followed initially by a gradual slowing in the rate of escape rhythm and then by a sudden increase in the R-R interval to three times the control value. In the fifth patient (Case 18), the transvenous pacemaker, set in the demand mode at a rate of 30 beats/min, suddenly took control of the ventricle during the injection. The control rate of escape rhythm was 40 beats/min. There was no appreciable change in the rate of escape rhythm before the artificial pacemaker started to control the ventricle. The plasma lidocaine level in this patient, obtained 1 minute after the end of the 110 mg bolus injection, was 7.5 μg/ml.

Side effects: Hypotension was not observed in any patient. Two patients became drowsy during the study. One patient complained of tinnitus immediately after the bolus injection. All the untoward effects were transient.

Discussion

It is generally believed that the use of lidocaine is contraindicated in patients with complete atrioventricular (A-V) block without the prior insertion of a ventricular pacemaker. This opinion is based on studies showing that lidocaine suppresses diastolic depolarization in Purkinje fibers[1,2] and slows the ventricular rate in dogs with surgically induced A-V block.[3] Lidocaine has also been demonstrated to cause slight and inconsistent changes in the diastolic threshold of excitability[4,9] and to worsen intraventricular conduction in some patients with preexisting intraventricular conduction disturbances.[4–8] However, there are only two studies[1,5] in which the effects of lidocaine were studied in patients with complete A-V block. In one,[5] a 1 to 2 mg/kg bolus injection of lidocaine delayed the return of the intrinsic ventricular rhythm after the abrupt cessation of ventricular pacing in three of six patients studied. In the other,[1] an intravenous bolus injection of 100 mg of lidocaine caused no slowing of the rate of the escape rhythm in the five patients studied.

Patients with no slowing or slight and transient slowing of ventricular escape rate (Group I): In our study, therapeutic doses of lidocaine caused no slowing of the rate of escape rhythm in 3 of 18 patients. This result was similar to that of Roos and Dunning.[1] In 10 other patients, slight and transient slowing occurred either during or within 3 minutes of administration of the bolus dose and lasted approximately 5 minutes. This result was similar to the results obtained in the dog studies.[4]

The minimal or absent slowing of the escape rate observed in the majority of our patients and in those described by Roos and Dunning[1] suggests that either

the lidocaine blood levels were inadequate to suppress diastolic depolarization or that the ventricular escape pacemaker was insensitive to the effects of lidocaine. The first possibility is probably untenable because Roos and Dunning[1] found no change in the rate of escape rhythm when blood levels were in excess of 20 μg/ml. This finding suggests that the ventricular escape pacemaker was relatively insensitive to the effects of lidocaine. Such insensitivity would be expected if the ventricular escape pacemaker were due to slow channel-dependent activity such as that postulated to be responsible for the pacemaker activity of the sinoatrial node,[9] the spontaneous activity found in the mitral valve leaflets,[10] the transient low amplitude depolarization induced by digitalis[11] and the spontaneous activity in ventricular muscle induced by depolarizing current.[12,13] This type of spontaneous activity, in contrast to that induced in Purkinje fibers by stretch[1] or by exposure to perfusing solutions containing a potassium concentration of less than 3 mEq/liter,[2] has been found to slow only slightly after the administration of lidocaine.[13,14]

In this regard, the effects of lidocaine on sinus rate are pertinent to our study. Usually lidocaine causes no change in sinus rate.[9,15] However, both an increase and a decrease in sinus rate have been reported. The increase occurred in patients with sinus bradycardia associated with myocardial infarction and was attributed to a vagolytic action.[16] Sinus arrest has been reported in three patients.[17–19] In two, sinoatrial block was present before the administration of lidocaine[17,18] and one of these patients[18] was also treated with quinidine. The third patient had sustained an acute inferior wall infarction and was being treated with diphenylhydantoin. In these patients, it is possible that conduction block of the sinus impulse in the perinodal fibers, like that observed in isolated rabbit hearts,[14] was the responsible mechanism.

TABLE II
Summary of Previously Reported Data

			Intraventricular Conduction			
			Before Lidocaine		After Lidocaine	
Authors	Lidocaine Dose	Peak Blood Level (μg/ml ± SD)	Finding	no. of Patients	Finding	no. of Patients
Roos and Dunning[1]	100 mg/20 sec	26.6 ± 2	Normal H-V	12	No change in H-V	12
			Prolonged H-V	26	No change in H-V	19
					Lengthening of H-V	7
			Complete A-V block (distal to His in 4)*	5	No effect on escape rate	5
Kunkel et al.[24]	6 mg/kg per 22 min	6.2 ± 0.84	Normal H-V	4	No change in H-V	4
			Prolonged H-V	4	No change in H-V	4
Gupta et al.[6]	50 to 100 mg bolus dose	. . .	Prolonged H-V	16‡	H-V increased 5 to 10 msec	1†
					2° to 3° A-V block distal to His	2
					2° A-V block distal to His on atrial pacing	1
					No change in H-V	12
			Normal H-V	4‡	No change in H-V	4
			Atrial fibrillation, alternating RBBB and LBBB	1	Asystole with occasional ventricular escape	1
Liss et al.[7]	80 mg bolus dose	. . .	Bifasicular block associated with acute anterior infarction	1	Complete A-V block and asystole	1
Rosen et al.[25]	50 mg bolus dose ± additional 100 mg bolus dose	. . .	Prolonged H-V	1	No change in H-V	1
			Normal H-V	9	No change in H-V§	9
Bekheit et al.[26]	100 mg/l min	. . .	Normal H-V	5	No change in H-V	5

* = pre-lidocaine H-V interval not determined in fifth patient.
† = pre-lidocaine H-V interval not reported in this patient.
‡ = all had electrocardiographic changes of bifascicular block.
§ = 4 patients had increased H-S interval (His spike to end of S wave) after lidocaine.
A-V = atrioventricular; LBBB = left bundle branch block; RBBB = right bundle branch block; SD = standard deviation.

Patients with abrupt slowing of escape rate (Group II): The lidocaine-induced abrupt prolongation of the R-R interval to approximately two or three times the length of the immediately preceding interval observed in our Group II patients may also have been due to conduction block rather than to a decrease in the rate of impulse formation. The results of studies in ventricular fibers[20,21] and in situ dog hearts[22,23] predict that lidocaine might cause slowing of conduction in the zone surrounding an ectopic ventricular focus if the zone were partially depolarized. It is possible that the different effects of lidocaine in our Group I and Group II patients reflect a greater degree of partial depolarization in the fibers surrounding the ectopic pacemaker of the patients in Group II than of those in Group I. Exit block may also have contributed to the delayed return of the intrinsic ventricular rhythm after cessation of ventricular pacing in the patients studied by Ryden and Korsgren.[5] This postulated mechanism may also apply to the reports of lidocaine-induced complete A-V block. Table II,[24–26] which summarizes these cases, shows that all patients who had complete A-V block after administration of lidocaine had preexisting conducting system abnormalities, manifested by bundle branch block or prolongation of the H-V interval, or both. Table II also shows that lidocaine caused further impairment of intraventricular conduction in only a small percentage of the patients with conduction abnormalities, just as lidocaine caused marked slowing of the ventricular rate in only 5 of our 18 patients with distal His bundle block.

Roos and Dunning[1] suggested that the deleterious effects of lidocaine on intraventricular conduction in patients with prolonged H-V intervals are caused by the rapid achievement of a critically high plasma lidocaine level. Our results suggest that the induction of conduction block depends more on a critical degree of preexisting conduction impairment than on a rapidly achieved critically high blood level. Our argument is supported by the following observations: (1) Nineteen of the 25 patients with prolonged H-V intervals described by Roos and Dunning[1] and 12 of the 16 patients with such intervals described by Gupta et al.[6] showed no further intraventricular conduction delay after administration of lidocaine even though the rate of lidocaine administration and the blood levels achieved[1] were the same as in patients with higher degrees of A-V conduction delay; and (2) the sudden decrease in the rate of the escape pacemaker shown in Figure 3 was the same after two different rates of lidocaine administration and occurred when the lidocaine blood levels were low.

Identification of patients prone to have abrupt rate slowing after lidocaine: Our study and those referred to in Table II demonstrate the difficulty in identifying the patients who will be deleteriously affected by lidocaine. In our study, the site of block was located distal to the site of the His potential recording in all 13 patients who underwent such studies, but only 5 of the 13 manifested the abrupt slowing of the rate suggestive of exit block. Moreover, although four of the five patients described by Roos and Dunning[1] had distal His bundle block, none manifested abrupt slowing of the escape rate. The duration of the QRS complex and the rate of the escape rhythm were also of no value in identifying the patients prone to experience abrupt rate slowing.

Implications: Our results may be pertinent to an understanding of the antiarrhythmic effects of lidocaine. The ventricular escape rhythm associated with complete distal His block is one of the few situations in which an ectopic rhythm can be attributed with certainty to automaticity. Although the mechanism for enhanced automaticity in other clinical settings may be different from that responsible for the escape pacemakers in our patients, our results suggest that the antiarrhythmic effect of lidocaine is due more to its ability to depress conduction than to its ability to suppress automaticity. The inability to determine with certainty whether lidocaine-sensitive arrhythmias are due to enhanced automaticity or to reentry makes accurate analysis of lidocaine's antiarrhythmic effects difficult.

Acknowledgment

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Threshold Behavior of Electrodes in Long-Term Ventricular Pacing

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In a study of the electrical stimulation threshold behavior of electrodes in long-term ventricular pacing, 120 patients were followed up for a minimum of 5 years after initial pacemaker implantation (range 5 to 11.3 years). In each patient, at least two postimplantation threshold measurements in milliamperes at a pulse duration of 1 msec were obtained at the time of pulse generator replacement. A plot of 380 long-term thresholds showed stability in 97 (81%) of the 120 patients. Four subgroups, each exhibiting a different threshold pattern, were analyzed separately. An unexplained progressive increase in threshold occurred in 23 patients (19 percent).

An additional 297 patients with low output or programmable pacemakers were assessed noninvasively for threshold variation for 1 month to 4 years after pacemaker implantation. None showed threshold increases of more than 2.5 milliamperes. Evaluation of 22 patients with Medtronic 5816 bipolar electrodes, attached to Medtronic 5870 capacitor discharge pulse generators, revealed high thresholds in 14 (64 percent), electrode removal for failure to pace was required in 9 (41 percent). Direct current leakage related to specific pacemaker circuits in these pulse generators (capacitor discharge) may be one cause of high threshold in these electrodes.

The data indicate that there is overall threshold stability up to 11 years after pacemaker implantation and support the use of the newer low output pulse generators with increased longevity.

The success of long-term pacemaker therapy is dependent on the quality of energy sources, pulse generator electronics, adequate patient follow-up and electrode factors of which the electrical stimulation threshold is of major concern. Knowledge of long-term threshold behavior is imperative for selection of generator output, maximal utilization of the pulse generator and avoidance of system failures caused by electrode failure, especially in view of the availability of generators with increased longevity. Threshold is the least current, voltage or energy needed to provoke contraction of the tissue stimulated, and its long term behavior determines the design and longevity of pacemakers and their power sources. If the long-term threshold does not remain stable but rises with the passage of time then implanted long-term power sources will fail to pace.

Initial changes in threshold after implantation have been well documented.[1–14] Because of tissue reaction around the electrode tip, threshold rises 1 to 2 weeks after implantation, declines slightly and then stabilizes within several months to a level two or three times that of the initial value. Opinions concerning long-term threshold behavior are widely dissimilar, with some reports[15–22] indicating that thresholds rise continuously after implantation or after initial stabilization. This study presents a group of patients whose pacing threshold was examined at the time of pulse generator replacement at least twice 5 to 11 years after initial pacemaker implantation.

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TABLE I
Types of Electrodes Used in 120 Patients

Group	Threshold Behavior	Cases (no.)	Endocardial						Myocardial	
			Cordis Unipolar				Medtronic Bipolar			
			2 mm	4 mm	6 mm	CL	5816	6901	Unipolar	Bipolar
I	Stable	51	13	23	1	5	1	1	5	2
II	Decreasing	20	3	12	0	0	0	2	3	0
III	Stable, variable	26	4	16	0	0	3	0	3	0
IV	Increasing	23	8	9	0	2	2	2	0	0
Total	...	120	28	60	1	7	6	5	11	2

CL = continuous lead.

Materials and Methods

Study Group

One hundred twenty patients with a pacemaker implanted at Montefiore Hospital and Medical Center from January 1960 to January 1971 met the following criteria:

1. The initial implantation and all subsequent pulse generator replacements were performed by us.
2. A minimum of two long-term threshold measurements were obtained; that is, at least three operative procedures were performed, including the initial implantation.
3. The same electrode was used without revision of ventricular position for a minimum of 5 years and the last data point was obtained after this time.

The remaining patients with pacemaker implantation were excluded from the study for the following reasons:

1. They died before all criteria were met.
2. An electrode was removed because of irreparable fracture or infection.
3. The longevity of a pulse generator extended beyond the time limit of the study so that a post-5 year data point was not obtained. For example, a patient whose pulse generator was replaced 4 years after implantation would not have been included until the new pulse generator was replaced (perhaps 7 to 8 years after implantation).

Current thresholds were measured at the initial implantation and during operative pulse generator replacement. No noninvasive measuring techniques were used.

A battery-operated constant current generator, built by us and frequently calibrated, capable of producing unidirectional regulated outputs at step increments of 0.1 milliamperes (ma) to a maximum of 19.9 ma, was used to measure thresholds. Electrode impedance at 10 ma and 1 msec pulse duration was simultaneously determined. Pulse durations were at 1 or 2 msec for measurements obtained before 1973 and at 0.5, 1 or 2 msec subsequently. Thresholds were determined by stepwise decrease of current until capture no longer occurred.

For purposes of uniformity, all reported current thresholds are expressed in milliamperes at pulse duration of 1 msec. Each electrode model has a different threshold, a function of its surface area, so that each electrode was its own control and only long-term thresholds were reported. The threshold at implantation was disregarded for this study, and each initial long-term threshold measurement was considered as 100 percent, and all subsequent thresholds, increasing or decreasing, were compared as a percentage. Except for the 6 mm, all Cordis electrodes included in the study are still commercially available. The bipolar Medtronic model 5816 is no longer being manufactured, although many presumably remain in service. All myocardial lead models are still available. The Cordis continuous lead (CL) and Medtronic 6901(7) electrodes are now most frequently used by us but have not been available long enough to be represented in the study group. Each patient had a minimum of two and 80 percent had three or more long-term data points. A total of 380 long-term measurements were made in the 120 patients.

Several types of electrodes were used in this study; 107 were unipolar or bipolar endocardial electrodes positioned in the apex of the right ventricle; 13 were myocardial left ventricular (11 unipolar and 2 bipolar) (Table I).

Anesthesia was not a variable. All pulse generator replacements were performed with 2 percent piperocaine hydrochloride applied locally.

Additional Patients

An additional 297 patients were studied because they had one of three different pulse generators, one with a very low output and two with a noninvasively variable output. All patients with 1 month to 4 years of follow-up used the Cordis Stanicor 143N, Omni-Stanicor 162C and 162D and the Medtronic 5931 and 5961 pacemakers. The Cordis Stanicor 143N model has a current limited output of 3.0 ma at 6.5 volts (v) at a pulse duration of 1 msec (19.5 microjoules [μJ]). The Omni-Stanicors 162C and 162D have programmable output currents and rates, with a maximal output voltage of 6.5 v. Current settings are at 9 ma (high), 6 ma (medium), 4 ma (low) and 2.3 ma (test). For rates of 60, 65, 70, 80, 90 and 100 pulses/min, the pulse durations are 2.0, 1.8, 1.7, 1.3, and 1.2 msec, respectively, so that 24 different output steps are available from a maximum of 9 ma at 2 msec pulse duration at 6.5 v output (setting is high, rate 60, 117 microjoules) to a minimum of 2.3 ma at 1.2 msec pulse duration at 1.15 v output (setting is test, rate 100, 3.2 μJ). The Medtronic 5931 and 5961 units have an adjustable pulse duration from 0.05* to 1.7 msec, a rate of 70 pulses/min, current output of 10.4 ma and voltage output of 5.2 v (minimum 2.7 μJ, maximum 91.9 μJ). All except the the Stanicor 143N have adjustable outputs for thresholds measured noninvasively.

These pulse generators have not been in use for a sufficient duration to meet the criteria of the post-5 year group. Nevertheless, because of the very restricted output of the Stanicor 143N and the output variability of the OmniStanicor and Medtronic models 5931 and 5961, they offered the possibility of a practical evaluation of the clinical observation that thresholds stabilize at a low level and remain there chronically. Three of the models (OmniStanicor, Medtronic 5931 and

* Pulse duration of 0.05 msec supplied by the manufacturer at our request.

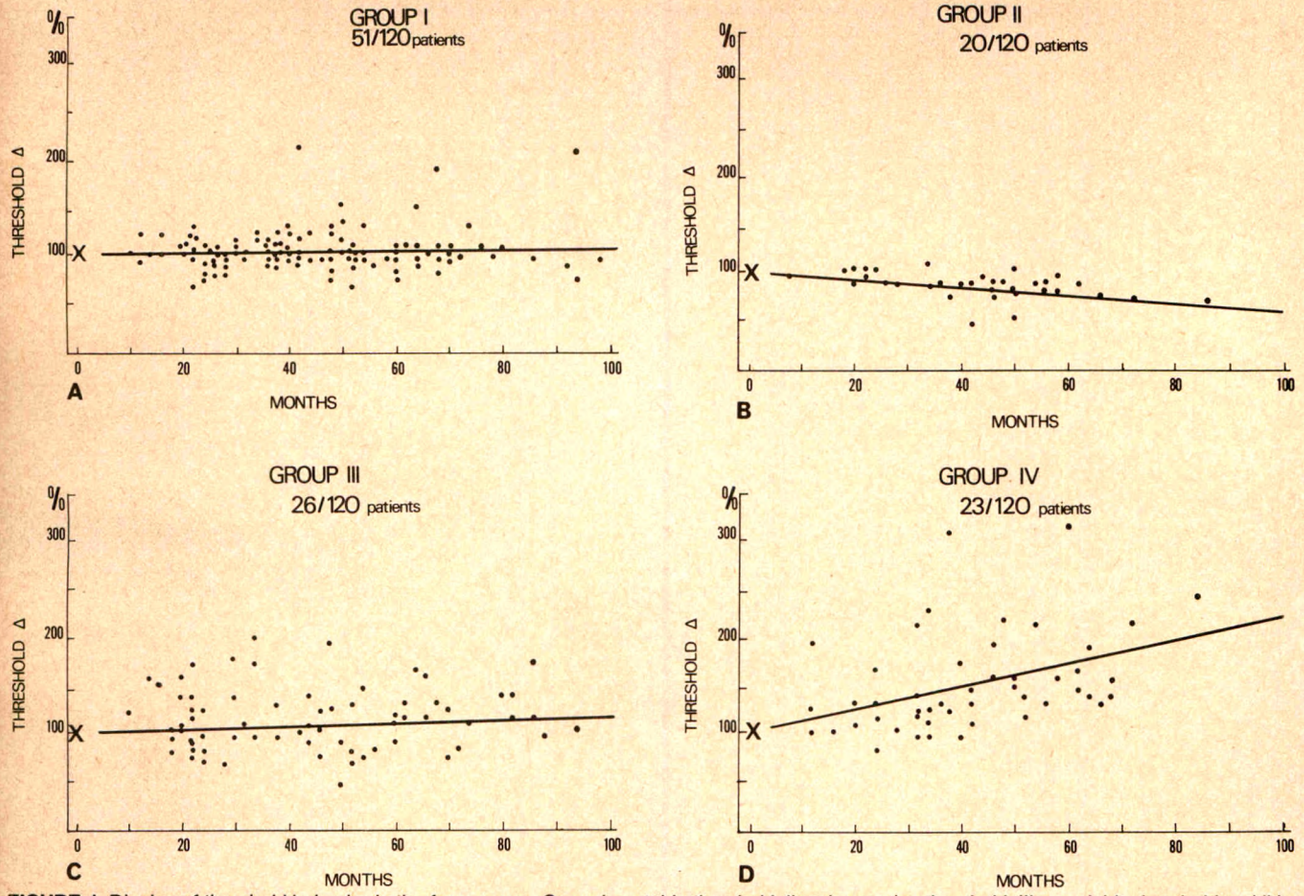


FIGURE 1. Display of threshold behavior in the four groups. Group I = stable threshold; II = decreasing threshold; III = variable threshold and IV = increasing threshold. Note the scatter of data points. Point **X** represents the 100 percent figure for all patients in a group.

5961) allow noninvasive threshold evaluation during follow-up in addition to that at pulse generator replacement. Further, the OmniStanicor units were allowed to pace chronically at a rate of 70 pulses/min at the test output (2.3 ma, 1.7 msec and 1.15 v equal to 4.5 μJ) and the Medtronic units at a rate of 70 pulses/min at a pulse duration of 0.2 msec (10.4 ma, 0.2 msec and 5.4 v equal to 11.2 μJ). With so low an output, the long-term rise in threshold would immediately manifest itself clinically. The universal absence of clinical failure to pace because of threshold increase, long-term stability of the threshold as a function of pulse duration (Medtronic) and chronic maintenance of threshold below 3.0 ma (Cordis 143N) indicated that the long-term threshold was stable, at least before 5 years after implantation.

Data Tabulation

To establish linear representation, the first long-term data point in each patient was normalized to a unit value (100 percent), irrespective of the time elapsed since the initial implantation. Each subsequent threshold in the same patient was divided by this first long-term value. In this way, stable thresholds appear as a straight line plotted against time. Any slope reflects a change in threshold. Inclusion of short- to long-term threshold changes would have required a curvilinear graph and would not be relevant to this analysis. Results are expressed in percent changes of threshold versus time in months after the first long-term data point (first pulse generator replacement). The first point on each graph thus represents the 100 percent threshold for *all* patients in that group.

Linear regression equations, based on a least squares criterion, yielded slopes and standard errors.[23]

Results

Study group: None of the 297 additional patients had long-term increases in threshold. The 120 (5 year) study patients were separated into four groups after analysis of the individual data.

Group I: Fifty-one patients, 43 percent of the total, had a substantially stable threshold, an upward slope of only 0.7 percent annually and a small average standard error of ±0.7 percent (Fig. 1A).

Group II: Twenty patients, 17 percent of the total, had a decreasing threshold with a negative slope of 5 percent annually and an average standard error of ±0.6 percent (Fig. 1B).

Group III: Twenty-six patients, 22 percent of the total, had a threshold that varied widely about a stable mean. Without the last threshold point one would have assumed that the threshold was increasing or decreasing. The overall slope was upward at 1.9 percent annually and the average standard error was ±1.3 percent (Fig. 1C).

Group IV: Twenty-three patients, 19 percent of the total, had a constant rise in threshold with an annual rate of increase of 14 percent and an average standard error of ±2.4 percent (Fig. 1D).

Groups I, II and III contained 97 patients, 81 percent of the whole, with an upward slope of 0.4 percent annually, follow-up periods ranging up to 11 years after implantation and an average standard error of ±0.6 percent.

Medtronic 5816 bipolar electrode: The peculiarities of this electrode are of interest. Twenty-two leads implanted during 1965 to 1967 had been attached to Medtronic model 5870 pacemakers characterized by a relatively high output (13.0 ma, 6.5 v, 2 msec pulse duration, equal to 169 μJ). Nine electrodes (41 percent) were removed because of an increase in threshold beyond the output capacity of the pulse generator. Their implanted longevity ranged from 1 to 100 months (mean 41 months). Five other electrodes had high and increasing thresholds, but in four cases the patient died of causes unrelated to pacing before the electrode required removal. In eight cases (36 percent) a normal threshold was recorded.

Six of the 22 patients with this electrode are included in the study group (Table II). Two of the six died before electrode removal and each had a high variable electrode threshold; one is active with a progressive threshold increase, one required electrode removal for high threshold, and two have a stable threshold.

TABLE II
Long-Term Threshold Behavior in 120 Patients Followed Up for 5 Years

Group	Threshold Behavior	Patients		Slope (% change per year ± standard error)
		no.	%	
I	Stable	51	43	+0.7 ± 0.7
II	Decreasing	20	17	−5.0 ± 0.6
III	Stable, variable	26	22	+1.9 ± 1.3
IV	Increasing	23	19	+ 14 ± 2.4
I, II, III	...	97	81	+0.4 ± 0.6
I, II, III, IV	...	120	100	+2.4 ± 0.7

Discussion

Long-term threshold behavior: Groups I and II had the most favorable threshold patterns and accounted for 59 percent (71 of 120) of all patients. In Group III, although all patients had a minimum of three long-term data points, the threshold trend was dependent on the most recent measurement. This pattern accounted for the wider standard error around the mean. Some cases in Group III may merge into Group IV if the trend remains upward, or into Group I or Group II if stabilization or decrease occurs. The appearance of erratic but largely stable patterns may be explained by undetected physiologic or pharmacologic variations at the time of measurement. In Group IV, representing 19 percent of cases (23 of 120), there was a striking threshold increase of 14 percent (standard error ±2.4) annually and the pattern closely resembled that of *total* long-term behavior reported elsewhere.[16,17]

No specific correlations with factors such as heart size or medication were found. The distribution of types of electrodes (Table I) did not vary significantly within each group. In contrast to the suggestion of others,[14,16,17] initial thresholds had no preferential effect on the course of late threshold behavior.

Our data are directly at variance with recent reports[16,17] suggesting a 15 percent annual rise in threshold for all cases. The latter reports were partially derived from studies with the EM 169 Variopacemaker (Siemens-Elema), which allows noninvasive magnetic induction of a fixed rate of 100 pulses/min with a 15 step decrease in voltage (0.35 v decrements) and permits determination of the voltage threshold.[15–17,24] Noninvasive techniques were not used in our study except with three of the four pacemaker models described in the additional group with less than 5 years of follow-up. Noninvasive threshold measurements are of unquestionable value in modern pacemaker follow-up,[25,26] but they should not be equated with those determined intraoperatively with accurately calibrated measuring devices.

Short- versus long-term threshold values: It is generally agreed that several factors influence the threshold increase between the short- and long-term measurements. These include myocardial tissue reaction around the newly positioned electrode tip, output characteristics of the pulse generator, electrode type and impedance. However, in most studies the time of implantation has been too short to permit evaluation of true long-term behavior. One study in animals suggested an inevitable rise in threshold due to injury around the electrode tip,[22] but the current density used was much higher than that of our study and the findings cannot be correlated with our data.

It is possible that the greater output of earlier pacemakers using the Medtronic 5816 electrode had a long-term deleterious effect. The outputs of the 169 μJ Medtronic 5870C (manufactured 1968 to 1969) differs substantially from that of the 27 μJ Medtronic 5951 (manufactured since 1974).

Direct current leak during pulse generator malfunction: A recent report[27] establishes the existence of a direct current leak during pulse generator malfunction previously thought to be caused by battery failure. Leaks of this type are responsible for rapid electrode destruction and high threshold as well as prompt battery depletion. Pulse generators with capacitor discharge circuits are prone to have such leaks although capacitor charge circuits are not. Some of the high threshold behavior of the 5816 electrodes, all attached to 5870C pacemakers, may have been caused by direct current leaks. The course of 5816 electrode thresholds was dissimilar in another study.[28] In that investigation, pulse generators may have been removed electively before a greater incidence of current drain could occur. No other correlation between threshold rise and physiologic or electronic factors was ascertained.

Variations in threshold measuring techniques (differences in current, voltage, impedance) may preclude direct comparison of data, especially if electrode impedance fluctuates. Impedance neither varied nor showed a progressive increase with time[29] in our patients and has been reported to be stable in other studies.[30]

Clinical implications: Long-term threshold behavior plays an important role in pacemaker therapy utilizing the newer low output long term pacemakers. A progressive threshold increase could exceed pacemaker output and defeat efforts to provide long-term pacing without pulse generator replacement. Our data indicate that thresholds are essentially stable up to 11 years after initial pacemaker implantation in 81 percent of cases. This finding supports the argument for use of low output long-term pacemakers, which are now the only models available. However, strict surveillance and noninvasive determinations of threshold when possible are required to detect the remaining 19 percent of patients whose electrical stimulation threshold seems to rise chronically and inexplicably.

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Ability of Holter Electrocardiographic Recording and Atrial Stimulation to Detect Sinus Nodal Dysfunction in Symptomatic and Asymptomatic Patients With Sinus Bradycardia

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Holter electrocardiographic recording and functional testing (determination of corrected sinus recovery time and estimated sinoatrial conduction time) were performed in 51 patients with sinus bradycardia. Thirty-seven patients were symptomatic; eight were known to have the sick sinus syndrome before study. Electrocardiographic abnormalities diagnostic of the sick sinus syndrome were found with Holter recording in 20 patients. When abnormal functional testing was defined with currently used criteria (corrected sinus recovery time greater than 525 msec or sinoatrial conduction time greater than 120 msec, or both), 12 of the 20 patients with an abnormal Holter electrocardiogram had abnormal and 8 had normal functional testing (sensitivity rate 60 percent); 23 of the 31 patients with normal Holter recordings had normal and 8 had abnormal functional testing (specificity rate 74 percent). These criteria for abnormal functional testing gave an apparent false positive rate of 40 percent and a false negative rate of 26 percent, using Holter electrocardiographic abnormalities as the criteria for sick sinus syndrome. When abnormal functional testing was defined as corrected sinus recovery time greater than 600 msec or sinoatrial conduction time greater than 130 msec, or both, the sensitivity rate remained at 60 percent but the specificity rate increased to 94 percent and the false positive rate decreased to 14 percent. Functional testing and the Holter electrocardiogram in combination are more useful than either alone in revealing sinus nodal dysfunction in asymptomatic and symptomatic patients with sinus bradycardia. When corrected sinus recovery time greater than 525 msec or sinoatrial conduction time greater than 120 msec, or both, is used to define functional testing as normal, the combination of a normal Holter electrocardiogram and normal functional testing is strong evidence against significant sinus nodal dysfunction.

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The sick sinus syndrome is an electrocardiographically defined group of intermittent or persistent functional abnormalities[1] that include marked sinus bradycardia, sinoatrial arrest, sinoatrial exit block and the bradycardia-tachycardia syndrome.[2] Clinically, the syndrome is often associated with one or more nonspecific symptoms[2–5] including dizziness, syncope and palpitations, but these symptoms are not required for diagnosis. By contrast, sinus bradycardia is simply an awake resting sinus rate of less than 60 beats/min. It may be normal,[6–8] a physiologic effect of training[9] or a manifestation of sinus nodal dysfunction.[2–6] Mild sinus bradycardia is frequently noted in patients with the sick sinus syndrome when diagnostic manifestations of sinus nodal dysfunction are not evident. It may therefore be difficult to determine whether patients with mild or moderate sinus bradycardia and complaints of dizziness or palpitations have the sick sinus syndrome. Sick sinus syndrome may be present but not evident in the standard electrocardiograms, which

samples electrical activity only briefly and intermittently, or the symptoms may be unrelated to the sinus bradycardia.[7] Patients with these findings can be further evaluated for sinus nodal dysfunction with Holter electrocardiographic recording[10] and electrophysiologic or pharmacologic tests. This report presents our data concerning the ability of ambulatory electrocardiographic recording and electrical stimulation of the atria to detect sinus nodal dysfunction in patients with sinus bradycardia.

Methods

Patients: Fifty-one patients were referred to us because their primary physician noted evidence of sinus bradycardia in one or more electrocardiograms and suspected clinically significant sinus nodal dysfunction. The patients ranged in age from 19 to 85 years (mean 57 years). Eight of the 51 had electrocardiographic evidence of the sick sinus syndrome before our evaluation. For each patient, medical records were abstracted and stored in data files and all available electrocardiograms were examined. The number of electrocardiograms antedating referral ranged from 1 to more than 10 per patient. Thirty-nine of the patients were symptomatic, suffering from one or more of the following: weakness, dizziness, vertigo, faintness, syncope, palpitations and paroxysmal arrhythmia.

For our study, we defined the sick sinus syndrome as (1) sinoatrial arrest; (2) sinoatrial exit block; (3) marked sinus bradycardia (mean sinus rate less than 50 beats/min with a minimum of less than 40 beats/min sustained for at least 1 minute); or (4) bradycardia-tachycardia syndrome, that is, moderate or marked sinus bradycardia (mean sinus rate less than 50 beats/min) alternating with recurrent supraventricular tachyarrhythmias (often of two or more varieties). Referral electrocardiograms were not considered to show the sick sinus syndrome if sinoatrial exit block could not be distinguished with certainty from marked sinus arrhythmia. Because the sick sinus syndrome has historically been defined with electrocardiographic criteria alone[1] and does not require associated symptoms, patients were not classified on the basis of symptoms possibly attributable to sinus nodal dysfunction.

Holter recordings: Each patient underwent 12 continuous

TABLE I

Clinical, Holter Electrocardiographic and Electrophysiologic Findings in 51 Patients

Case no.	Age (yr) & Sex	Heart Disease	Heart Size	Symptoms	12 Hour Holter ECG: Minimal Heart Rate (beats/min)	12 Hour Holter ECG: SAA, SAEB, BTS	Mean SACT (msec)	Maximal CSRT (msec)
				Holter Electrocardiogram Negative for Sick Sinus Syndrome				
1	73M	U	N	N	44	N	48	200
2	20F	N	N	Palpitations	44	N	32	329
3	31M	N	N	Palpitations	44	N	61	323
4	49F	HCVD	N	Palpitations	45	N	110	593
5	75F	ASCVD	↑	Angina; palpitations	45	N	107	502
6	68M	U	N	N	45	N	122	428
7	34F	N	N	Syncope; palpitations	45	N	79	366
8	31M	N	N	N	47	Marked SA or 2:1 SAEB	111	443
9	76F	HCVD	↑	Angina; dizziness	47	N	101	414
10	61F	HCVD	N	Vertigo	48	N	100	261
11	70F	ASCVD	↑	Palpitations	48	N	114	308
12	74F	ASCVD	N	Syncope	50	PAT	131	418
13	77F	HCVD; AI	N	N	50	PAT	88	201
14*	85M	AS	↑	Dizziness; paroxysmal atrial fibrillation	50	N	32	1108
15	36F	CHD	↑	Dizziness; palpitations	50	N	87	215
16	67F	HCVD	↑	Palpitations	50	N	131	271
17	65M	U	N	Syncope	50	Marked SA or 2:1 SAEB	80	655
18	37M	WPW	N	N	53	N	98	379
19	69F	HCVD	N	Dizziness; PAT	53	N	106	441
20	23F	RHD	N	N	54	N	97	443
21	61F	HCVD	↑	Palpitations	54	N	109	479
22	67F	ASCVD	N	Angina	55	N	89	226
23	21M	N	N	Palpitations	55	N	49	189
24	67F	N	N	Syncope	55	N	107	537
25	65M	Cardiomyopathy	↑	Palpitations	55	N	83	394
26	65F	HCVD	↑	Syncope	57	APDs with pauses suggesting 1° SAEB	134	339
27	61F	N	N	N	58	N	119	339
28	35F	HCVD	N	Palpitations	58	N	75	348
29	49M	HCVD	↑	N	60	N	96	374
30	64M	ASCVD; AS	N	N except syncope secondary to transient CHB	60	N	91	267
31*	58M	HCVD	N	Asystolic syncope	70	N	94	231

TABLE I (continued)

				Holter Electrocardiogram Positive for Sick Sinus Syndrome				
32	55F	? Diphtheria	N	Palpitations; dizziness	12	SAA	83 with 2:1 SAEB	1153
33	66M	HCVD	↑	N	12	SAA	76	2642
34	77M	CSD	N	Syncope; palpitations	26	SAA; 2:1 SAEB; SAW; PAT	145	1037
35*	77M	AS	↑	Syncope	26	SAA; SAEB	>200	1376
36*	63F	? Diphtheria	↑	Bradycardia-related fatigue and dyspnea on exertion	30	SAW; 2:1 SAEB	51	3496
37*	79F	N	N	Dizziness; palpitations	35	SAA; 2:1 SAEB	73	1923
38	65F	HCVD	↑	N	35	N	91	352
39*	19M	N	N	N	38	SAA	106	1272
40	58M	CSD	N	N	38	N	102	425
41	37M	U	N	? Syncope	38	N	85	1254
42	71M	HCVD	N	Syncope	38	N	90	518
43	59F	N	N	Palpitations	38	N	61	484
44	78M	HCVD	↑	N	38	N	95	709
45	19M	N	N	Bradycardia-related fatigue and dyspnea on exertion	40	SAW; 2:1 SAEB	86	22
46*	62M	HCVD	N	Paroxysmal atrial fibrillation and flutter	42	Recurrent PAT	187	726
47*	77M	N	N	PAT	44	Recurrent PAT	>170	474
48	52F	U	N	Dizziness	46	2:1 SAEB; recurrent PAT	75	424
49	54F	Pheochromocytoma	N	Palpitations	46	SAW	84	140
50	47M	CSH	N	Syncope	50	SAA	79	139
51	49M	HCVD	N	Dizziness	50	2:1 SAEB	112	1171

* Sick sinus syndrome in referral electrocardiogram.

AI = aortic insufficiency; APDs = atrial premature depolarizations; AS = aortic stenosis; ASCVD = arteriosclerotic cardiovascular disease; BTS = bradycardia-tachycardia syndrome; CHB = complete heart block; CHD = congenital heart disease; CSD = primary conduction system disease; CSH = carotid sinus hypersensitivity; CSRT = corrected sinus recovery time; ECG = electrocardiogram; HCVD = hypertensive cardiovascular disease; ↑ = increased; N = none or normal; PAT = paroxysmal atrial tachycardia; RHD = rheumatic heart disease; SA = sinus arrhythmia; SAA = sinoatrial arrest; SACT = sinoatrial conduction time; SAEB = sinoatrial exit block; SAW = sinoatrial Wenckebach phenomenon; U = heart disease of unknown etiology; WPW = Wolff-Parkinson-White syndrome.

hours of elctrocardiographic recording with an Avionics electrocardiocorder, model 350G. The tapes were reviewed on a model 650 Avionics Composite Electrocardioscanner. Mean heart rate was determined during the waking resting state. The Holter electrocardiogram was considered positive if it revealed one or more of the criteria of the sick sinus syndrome as defined.

Functional sinus nodal testing: All patients underwent right heart catheterization in the resting nonsedated postabsorptive state within 15 hours after the Holter electrocardiographic recording. All gave written informed consent. In a manner described previously,[5,11,12] two recording/stimulating catheters were positioned in the right atrium and atrial premature stimulation was performed. The responses to premature stimulation were analyzed to estimate mean unidirectional sinoatrial conduction time. Rapid atrial pacing for 30 to 60 seconds (30 and 60 seconds of pacing yields equivalent results) was performed at cycle lengths that allowed complete capture of the atrium, and the cycle length was progressively shortened to 400 msec; this sequence was repeated four times.

When atrial pacing was performed, the following intervals were measured: (1) the interval from the last driven atrial depolarization to the next spontaneous depolarization of any type, and (2) the interval from the last driven atrial depolarization to the next spontaneous P wave if this was different than the first interval. Sinus recovery time was defined as the interval from the last driven atrial depolarization during atrial pacing to the next spontaneous P wave if it appeared to be of sinus origin; corrected sinus recovery time was defined as sinus recovery time minus mean sinus cycle length[13] and maximal corrected sinus recovery time was defined as the longest recovery time observed at any pacing rate. Determination of the maximal corrected sinus recovery and sinoatrial conduction times is referred to in this report as functional testing and testing was considered positive if either interval was prolonged.

Results

Holter electrocardiogram: Of the 51 patients with sinus bradycardia studied, 20 had evidence of sick sinus syndrome in the Holter electrocardiogram (Table I); 31 had a normal Holter electrocadiogram and could not be classified as having sick sinus syndrome on the basis of the single 12 hour recording. The presence of symptoms, heart disease, advanced age and cardiomegaly was no more common in patients with an abnormal than in those with a normal Holter electrocardiogram (Table II), and sex distribution was similar in the two groups. Only 6 of the 20 patients with a positive Holter electrocardiogram had a definite diagnosis of sick sinus syndrome before referral, thus indicating that Holter monitoring is better than the standard electrocardiogram in detecting severe sinus nodal dysfunction in patients with sinus bradycardia. However, two of eight patients with recognized evidence of the sick sinus

TABLE II

Clinical Findings in 51 Patients With Holter Electrocardiograms

	12 Hour Holter Electrocardiogram			
	Negative for SSS		Positive for SSS	
	no.	%	no.	%
Cases (no.)	31	61	20	39
Symptoms	22	71	15	75
Heart disease	24	77	15	75
Female	18	58	7	35
Age >65 years	12	39	7	36
Enlarged heart	9	29	5	25
SACT >120 msec	4	13	4	20
Mean ± SD (msec)	93 ± 26.3		103 ± 40.0	
CSRT				
>525 msec	4	13	10	50*
Mean ± SD (msec)	388 ± 175		987 ± 853.3†	

* $P < 0.01$.
† $P < 0.001$.
CSRT = corrected sinus recovery time; SACT = sinoatrial conduction time; SD = standard deviation; SSS = sick sinus syndrome.

syndrome in prereferral electrocardiograms had a normal Holter recording.

Functional testing of sinus node[14] (Table III): When positive functional testing was defined by a corrected sinus recovery time greater than 525 msec (a criterion previously suggested by Narula et al.[13] and similar to that suggested by Gupta et al.[15]) or a sinoatrial conduction time greater than 120 msec (the upper limit of normal in normal patients[16,17] or for patients with only intermittent aymptomatic sinus bradycardia[5]), 12 of 20 patients with a positive Holter recording had positive functional testing and 23 of 31 with a negative Holter recording had negative functional testing. Thus, functional testing using these criteria had a sensitivity rate of 60 percent (12 of 20), a specificity rate of 74 percent (23 of 31) and an efficiency of 69 percent (35 of 51)[18–20] in recognizing sinus nodal dysfunction previously shown to be present with Holter monitoring. If the group with a normal Holter electrocardiogram were truly free of sinus nodal dysfunction, functional testing would have a false positive rate of 40 percent (7 of 20) and a false negative rate of 26 percent (8 of 31). However, some of the patients classified as having a false negative response using the abnormal Holter electrocardiogram as the criterion may not really have had a false negative response and most of the false positive responses (Table III) were probably not false positive (see Discussion).

Sensitivity and specificity of functional testing: The analysis of functional testing given in Table III used the most common criteria for abnormal functional tests. Changing the dichotomizing criteria of a test alters its sensitivity or specificity, or both. Accordingly, we tested the ability of different criteria to optimize the sensitivity or specificity of functional testing. The criteria for abnormal functional testing can be adjusted to give a sensitivity rate approaching 100 percent, a desirable change if functional testing is to be used as a *screening test* for sinus nodal dysfunction. We decreased the dichotomizing value for corrected sinus recovery time in

TABLE III

Functional Testing and Holter ECG Recording in 51 Patients

	12 Hour Holter Electrocardiogram		
	Positive	Negative	Total
*Functional test positive	12	8	20
Functional test negative	8	23	31
Total	20	31	51

Sensitivity = 12/20 (60%); Specificity = 23/31 (74%)
"False positive" = 8/20 (40%); "False negative" = 8/31 (26%)
Efficiency = $\frac{12 + 23}{51}$ (69%)

* Functional test "positive" if corrected sinus recovery time >525 msec *or* sinoatrial conduction time >120 msec, or both.

TABLE IV

Functional Tests as Screening Tests

	12 Hour Holter Electrocardiogram		
	Positive for SSS	Negative for SSS	Total
*Functional test positive	19	29	48
Functional test negative	1	2	3
Total	20	31	51

Sensitivity = 19/20 (95%); Specificity = 2/31 (6%)
False positive = 29/48 (60%); False negative = 1/3 (33%)
Efficiency = $\frac{19 + 2}{51}$ (42%)

*Functional test "positive" if corrected sinus recovery time >300 msec *or* sinoatrial conduction time >80 msec, or both.
SSS = sick sinus syndrome.

TABLE V

Functional Test as Tests for Exclusion

	12 Hour Holter Electrocardiogram		
	Positive for SSS	Negative for SSS	Total
*Functional test positive	12	2	14
Functional test negative	8	29	37
Total	20	31	51

Sensitivity = 12/20 (60%); Specificity = 29/31 (94%)
False positive = 2/14 (14%); False negative = 8/37 (22%)
Efficiency = $\frac{12 + 29}{51}$ (81%)

*Functional test "positive" if corrected sinus recovery time >600 msec *or* sinoatrial conduction time >130 msec, or both.
SSS = sick sinus syndrome.

25 msec steps and that for sinoatrial conduction time in 5 msec steps and computed rates for sensitivity, specificity and efficiency at each step. A sensitivity rate of 95 percent was considered reached when a corrected sinus recovery time greater than 300 msec or a sinoatrial conduction time greater than 80 msec was called abnormal. However, when these more sensitive criteria were used in our 51 patients (Table IV), the specificity of positive functional testing decreased to 6 percent (2 of 31) and the efficiency rate to 42 percent (21 of 51); the apparent false positive rate increased to 60 percent (29 of 48).

The criteria for abnormal functional tests can also be adjusted to optimize the specificity of such tests. This would be desirable if functional testing were to be used as a *test of exclusion,* that is, if functional testing were used to exclude the possibility of sinus nodal dysfunction when the Holter electrocardiogram is not available. Using such criteria, if functional tests are abnormal, the impression of sinus nodal dysfunction is reached with greater confidence. When abnormal functional testing was defined as a corrected sinus recovery time greater than 600 msec or a sinoatrial conduction time greater than 130 msec, or both, the specificity of functional testing in identifying patients with sick sinus syndrome documented with the Holter electrocardiogram increased to 94 percent (29 of 31) and the apparent false positive rate decreased to 14 percent (2 of 14). The real false positive rate must be even lower (see Discussion). With these more stringent criteria, the efficiency of functional testing increased to 81 percent (41 of 51) (Table V). Thus, these more stringent criteria are excellent for excluding sick sinus syndrome in patients for whom Holter monitoring is not available. Use of even more stringent values for each interval gave false negative results with documented sick sinus node.

Discussion

Repeated standard electrocardiograms may reveal only sinus bradycardia in patients who have symptoms suggestive of the sick sinus syndrome. Prolonged ambulatory Holter recording, although not invariably successful, is more useful in establishing the diagnosis in suspected cases.[2,10,21] Lipski et al.[10] performed Holter recordings in 55 symptomatic patients whose age range was virtually identical with that of our patients and found significant arrhythmias in 30 (55 percent). Of these 30 patients, 21 had marked sinus bradycardia or sinus arrest and 5 had bradycardia-tachycardia syndrome. By contrast, only an 11.5 percent incidence rate of sinus bradycardia or sick sinus syndrome, or both, was found in a group of patients who underwent Holter monitoring to evaluate chest pain, functional capacity or drug efficacy rather than for symptoms suggesting sick sinus syndrome.[22] The incidence of sinus nodal dysfunction revealed with the Holter technique is also small in asymptomatic subjects.[23,24] When the Holter electrocardiogram is positive, the diagnosis of sick syndrome is secure and functional testing (whether abnormal or normal) is not necessary to establish the diagnosis.

Invasive procedures utilizing atrial stimulation have been devised to detect abnormalities in sinus nodal automaticity and sinoatrial conduction. The precise frequency with which these tests are abnormal in patients with sinus nodal dysfunction is not certain but these tests, too, may fail to detect patients with severe sinus nodal dysfunction.[5,11,13,25] Because either ambulatory Holter monitoring or atrial stimulation when used individually can fail to demonstrate severe sinus nodal dysfunction in patients with sick sinus syndrome, we studied the ability of the combination of these two techniques to increase diagnostic reliability. Our results show that Holter electrocardiographic recording and functional testing together detect definite sinus nodal dysfunction more frequently (28 patients) than either method alone (20 patients each) in patients with sinus bradycardia and suggestive clinical symptoms. Similarly, the combination of sinoatrial conduction time and corrected sinus recovery time revealed abnormalities in our subjects more frequently than either determination alone.

Sensitivity and specificity of atrial stimulation technique: Some comment on apparent false negative and false positive functional testing is in order. A "false negative" test may occur in patients who have findings of sick sinus syndrome in the Holter recording because the functional defect, although not necessarily the anatomic one, is intermittent. This has been shown to be true for the atrioventricular (A-V) conduction system.[26] Such cases are not really false negatives. Also, functional testing may appear normal in the presence of sinus disease and sinus bradycardia because, although the sinoatrial conduction time is less than 120 msec, it would actually be prolonged if it could be corrected for the bradycardia.[5] In other instances, functional testing may be too insensitive to recognize a defect that is actually present; these cases are truly false negatives and probably constitute the majority of patients with positive Holter recordings and negative functional testing. Conversely, "false positive" functional testing (normal Holter electrocardiogram, abnormal functional testing) may occur because: (1) one or more 12 hour electrocardiographic recordings may not identify patients who have intermittent sinus nodal dysfunction (one of our patients [Case 14] whose sick sinus syndrome was established by electrocardiogram before referral had abnormal functional testing and a normal Holter electrocardiogram); (2) some functional abnormalities of the sinus node are not manifested in a Holter recording (for example, postpacing pauses or first degree sinoatrial exit block[12]); or (3) evidence of functional abnormalities characteristic of the sick sinus syndrome (such as sinoatrial Wenckebach phenomenon during marked sinus arrhythmia) may be present in the Holter recording but difficult or impossible to recognize. Therefore, the real false positive rate of functional testing is probably considerably less than the apparent rate obtained when the Holter electrocardiogram is used as the absolute criterion for the sick sinus syndrome. It is the fact that not all patients with a normal Holter recording are truly free of sinus node disease that makes the false positive

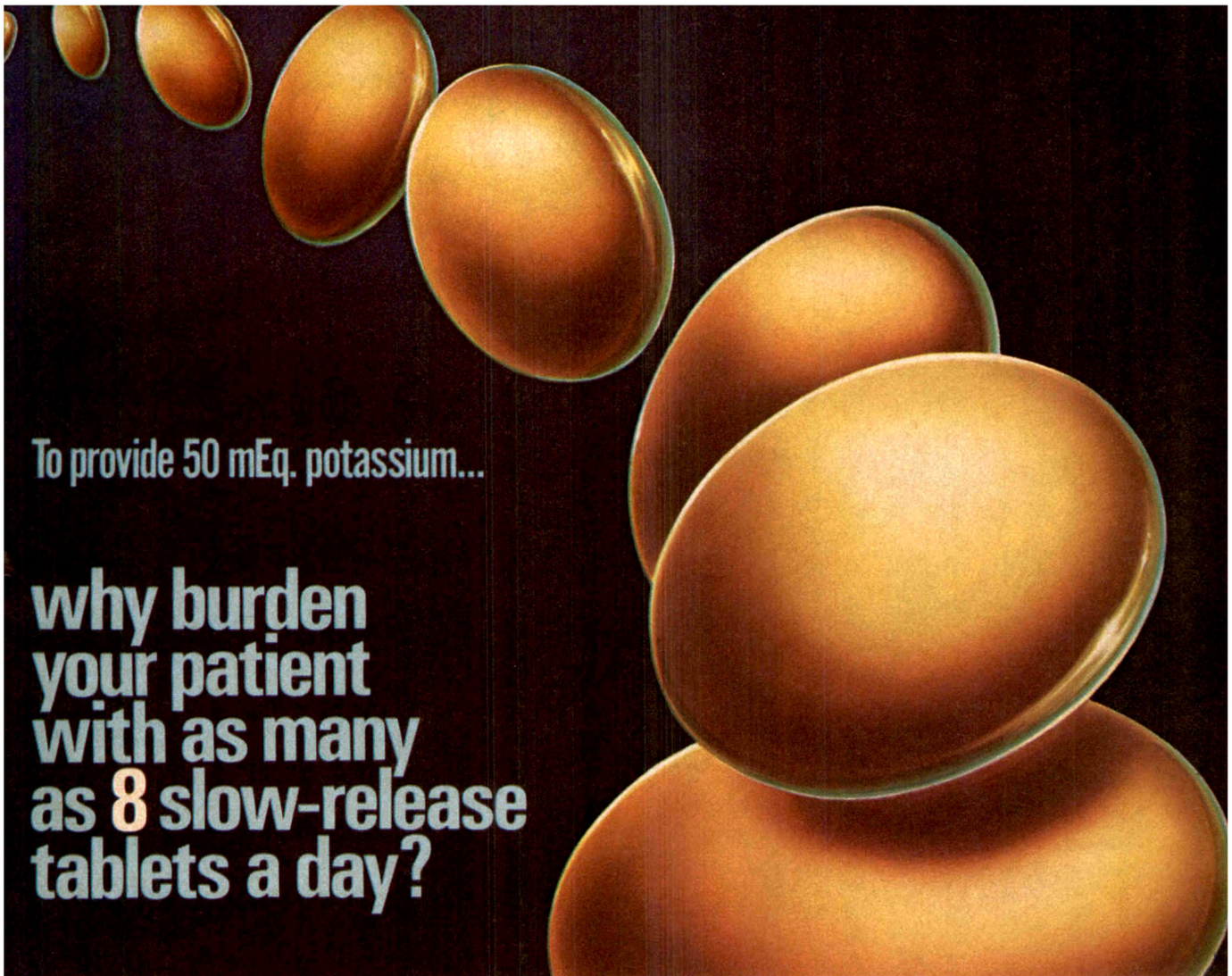
group more apparent than real and that makes functional testing complementary to Holter monitoring in the evaluation of patients with sinus bradycardia who are suspected of having the sick sinus syndrome.

Clinical implications: If functional testing and the Holter electrocardiogram are both normal (Tables III and V), is the patient free of clinically significant sinus nodal dysfunction? This is an important question to the clinician evaluating a symptomatic patient suspected of having such dysfunction. Some patients in this group may have the sick sinus syndrome as did one of our eight patients (Case 31) referred with established sick sinus syndrome. For such patients, either these tests are too insensitive or, more likely, the defects are intermittent. However, we believe that the overwhelming majority of patients with normal responses to functional tests and a normal Holter electrocardiogram do not have significant sinus nodal dysfunction. The combination of a normal Holter electrocardiogram and normal functional tests using standard criteria (corrected sinus recovery time greater than 525 msec or sinoatrial conduction time greater than 120 msec, or both) probably excludes significant sinus nodal dysfunction better than other available methods. With use of the more stringent criteria (corrected sinus recovery time greater than 600 msec or sinoatrial conduction time greater than 130 msec, or both), functional testing gives results that are about equivalent in specificity and sensitivity to those of a 12 hour Holter recording. Either Holter recording or functional testing used alone will fail to detect some cases of sick sinus syndrome.

Our results suggest that Holter electrocardiographic recording or functional testing will reveal sinoatrial nodal dysfunction in a large proportion of patients with sinus bradycardia and sick sinus syndrome and that either method is useful in distinguishing these patients from those with innocent sinus bradycardia. Functional testing with standard criteria is an excellent method of excluding sick sinus syndrome in patients with normal Holter electrocardiographic recordings. It is possible that use of additional tests (such as the response to atropine, isoproterenol or reflex maneuvers) with this combination will further improve the diagnosis of sick sinus syndrome.

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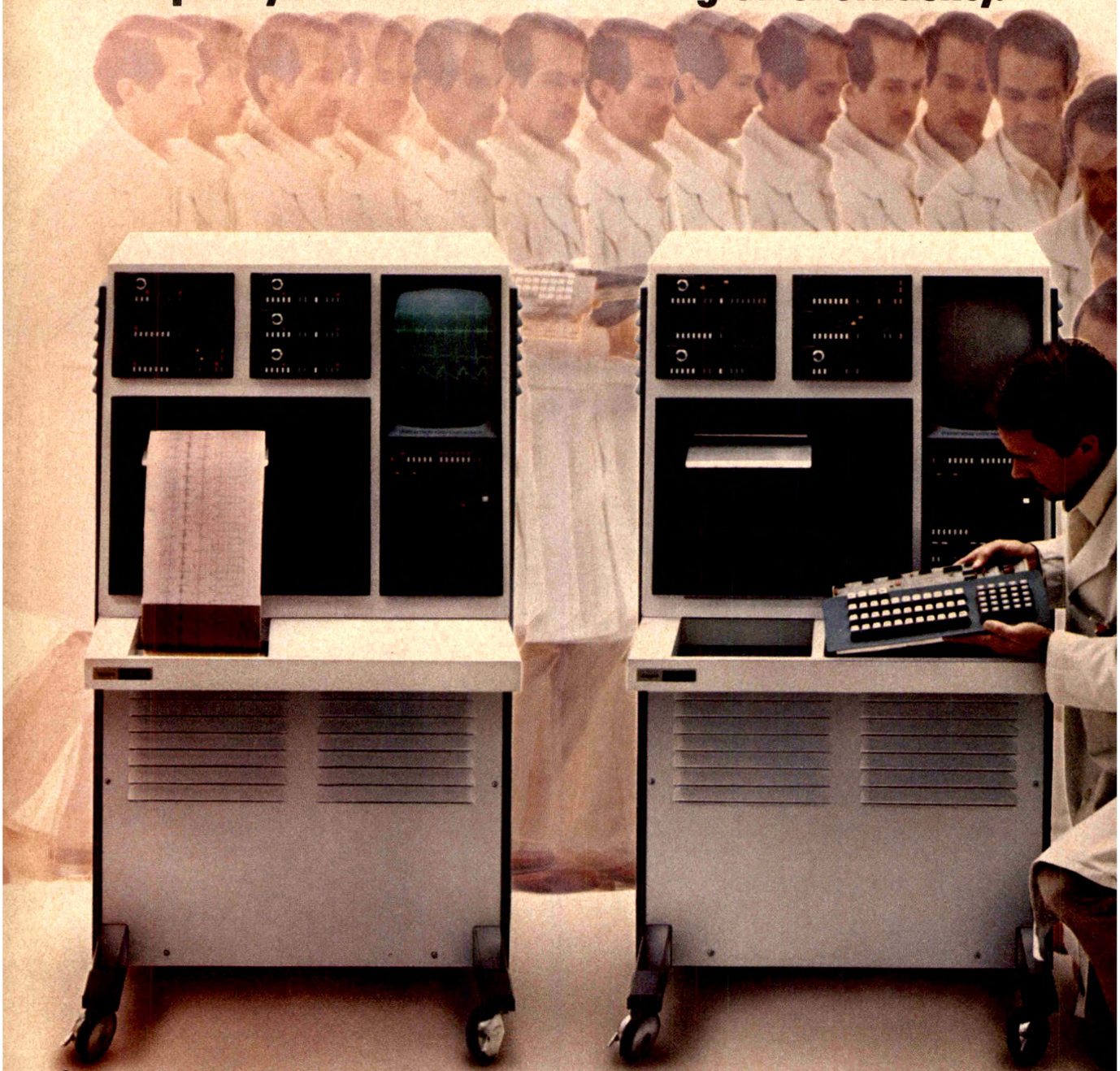
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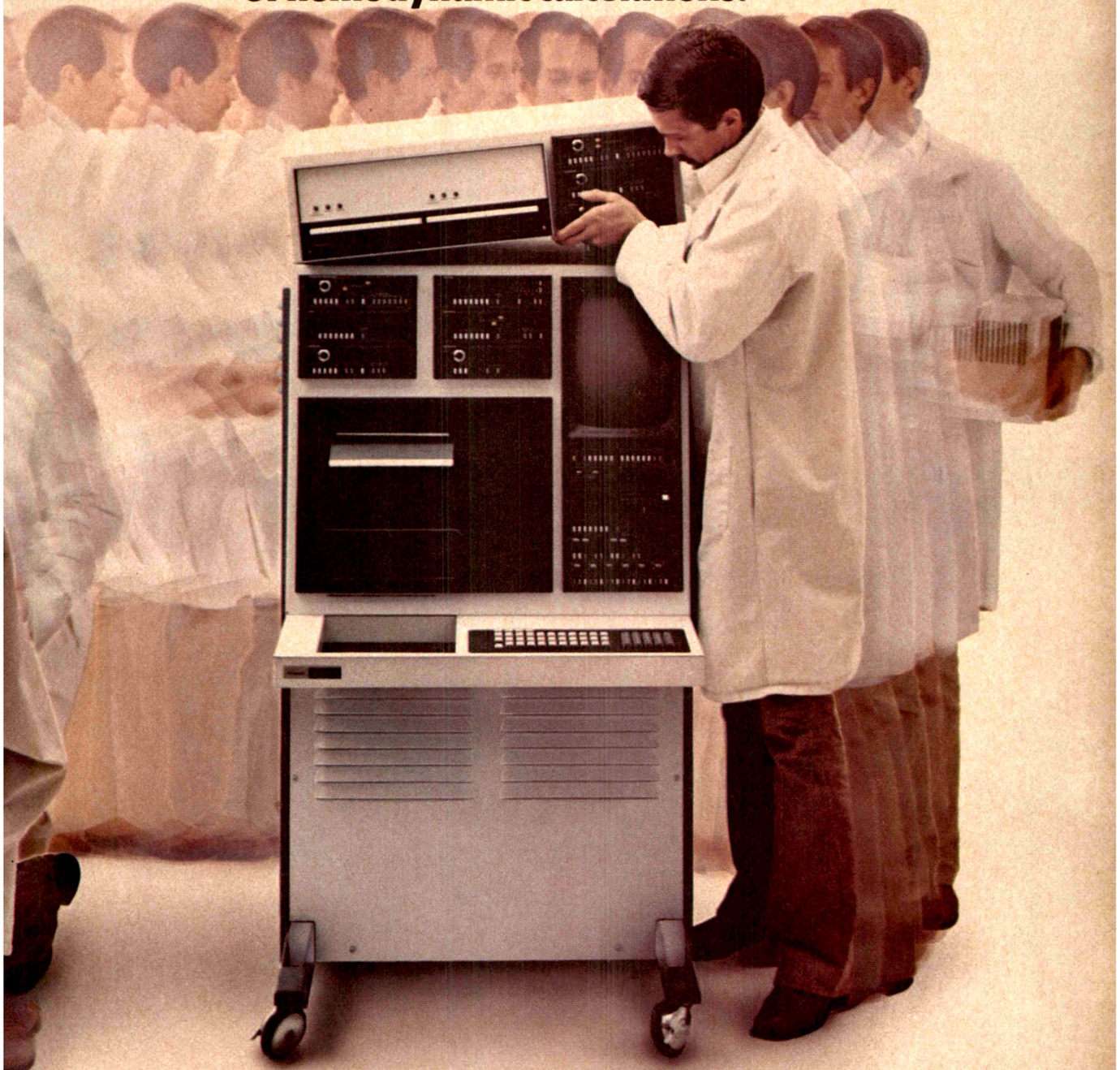
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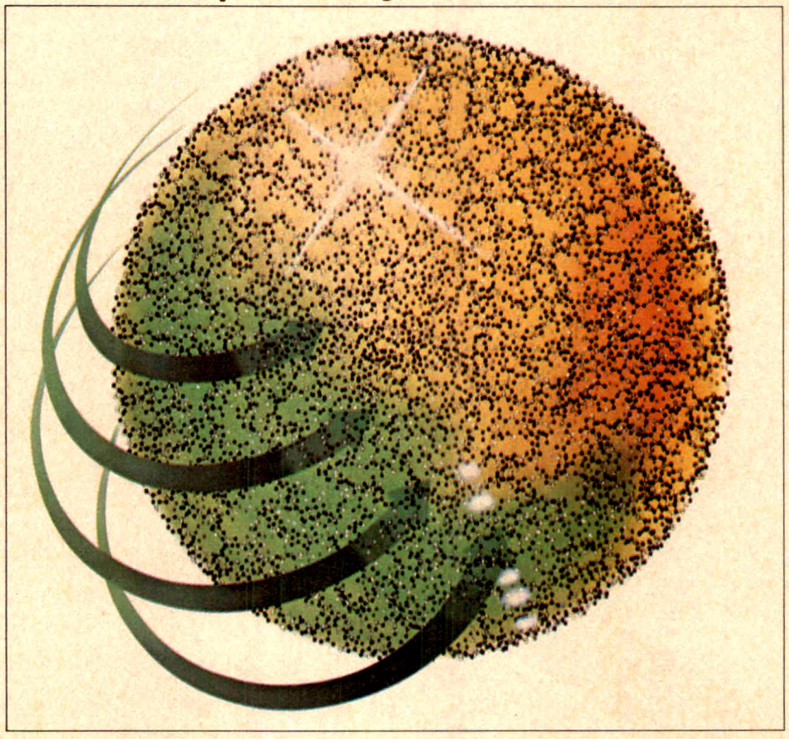
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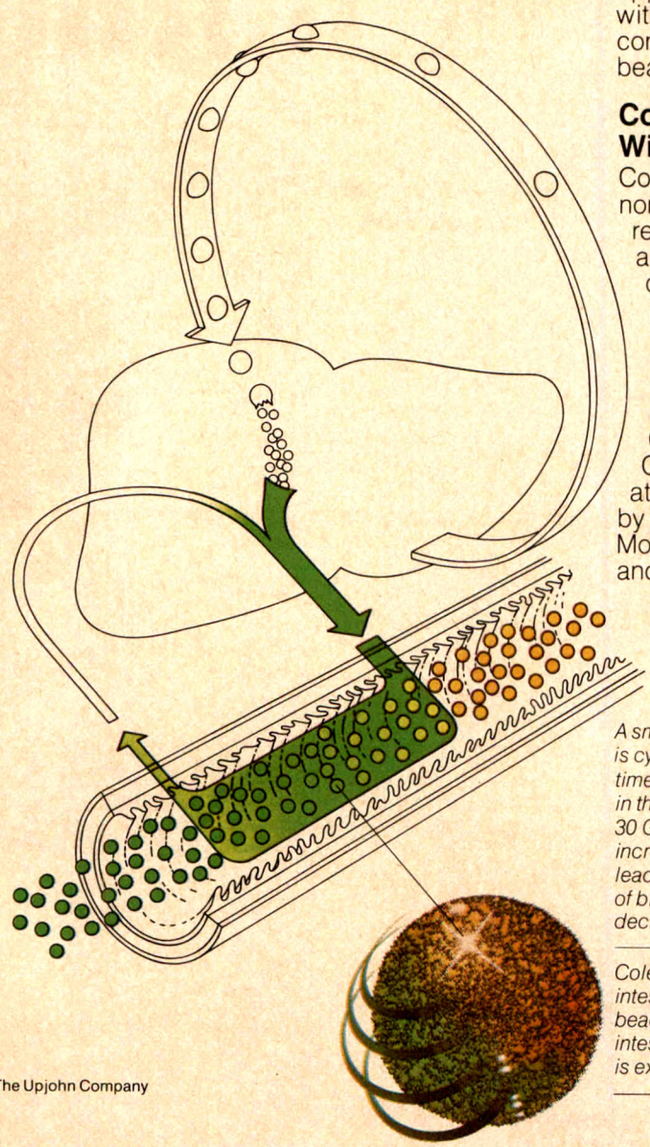
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The most common adverse reactions to Colestid are confined to the gastrointestinal tract. Constipation is the major single complaint, and at times is severe and occasionally accompanied by fecal impaction. Hemorrhoids may be aggravated. Most instances of constipation are mild, transient, and controlled with standard treatment.



A small pool of bile acids, about 2 to 4 Gm, is cycled through the intestine several times daily, and only about 0.6 Gm is lost in the feces. With Colestid therapy (15 to 30 Gm/day), the bile salt excretion is increased about 2 to 2½ times. This leads to increased hepatic production of bile acids from cholesterol, thereby decreasing serum cholesterol levels.

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Scope of Colestid Clinical Studies

One hundred and forty-four investigators and over 2,500 patients treated with Colestid (colestipol hydrochloride) participated in clinical trials of this new bile-sequestering agent. Thirty clinical studies helped to determine the efficacy, safety, and tolerance of Colestid in lowering serum cholesterol.

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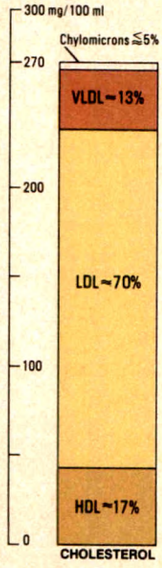
Colestid is indicated as adjunctive therapy to diet in the management of patients with elevated serum cholesterol due to primary hypercholesterolemia (elevated low-density lipoproteins).

The beta-lipoprotein (or low-density lipoprotein) transports most of the serum cholesterol, and it is believed that the fall in serum cholesterol with Colestid therapy is secondary to an increased clearance of the cholesterol-rich, low-density lipoprotein.

The reduction of serum cholesterol levels is usually evident within one month. When Colestid is discontinued, cholesterol levels usually return to baseline levels within one month.

Colestid has been shown to have no effect on, or to increase, triglyceride levels. Failure of cholesterol to fall or a significant rise in the triglyceride level should be considered as indication to discontinue Colestid.

Approximate contribution of the four lipoproteins to total serum cholesterol in a normal subject, fasting state.



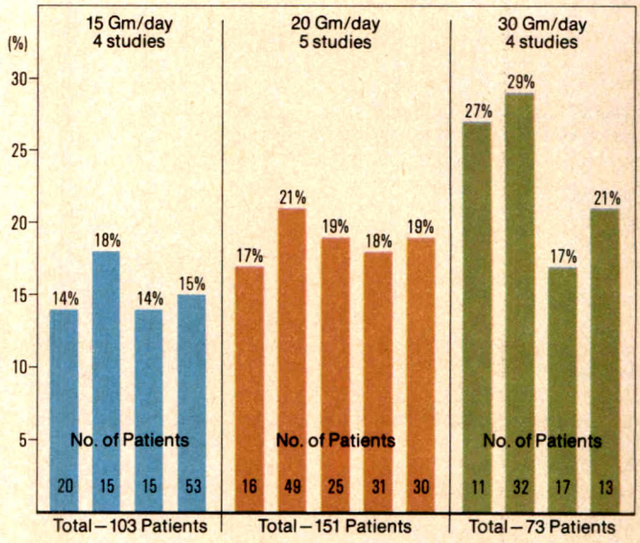
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Colestid 10 Gm twice a day is usually effective and avoids the obstacle of midday dosage. In general, however, Colestid dosage may be adjusted to meet the cholesterol-lowering requirements of the individual patient. For adults, the recommended dosage range is 15 to 30 Gm per day, divided into two, three, or four doses. To avoid accidental inhalation or esophageal distress, Colestid should not be taken in its dry form.

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Average Cholesterol Reduction at 15, 20, and 30 Gm daily



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The small particle size and neutral taste of Colestid (colestipol hydrochloride) make it a readily acceptable adjunct to your patient's diet. For example, it may be taken conveniently with orange juice in the morning and with applesauce at night. Colestid mixes easily with almost any liquid or pulpy fruit (such as milk, water, fruit juices, carbonated beverages, pineapple, applesauce, cereals, and soups).

Colestid is available in measured-dose packets of 5 Gm (30 to a carton) or in bottles of 500 Gm (with calibrated measuring spoon).

Drug Interactions

Patients should take other drugs at least one hour before or four hours after Colestid to minimize possible interference with their absorption.

Discontinuing Colestid could pose a hazard to health if a potentially toxic drug that is significantly bound to Colestid has been titrated to a maintenance level during Colestid therapy. Particular caution should be observed in digitalized patients, since there are conflicting results for the effect of Colestid on the absorption of digoxin and digitoxin.

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INDICATIONS AND USAGE Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long-term use.

Colestid (colestipol hydrochloride) is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low-density lipoproteins). It has been shown that Colestid has no effect on, or may increase, triglyceride levels.

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on morbidity or mortality due to atherosclerosis, including coronary heart disease. Investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS Colestid (colestipol hydrochloride) is contraindicated in individuals with hypersensitivity to any of its components.

WARNINGS TO AVOID ACCIDENTAL INHALATION OR ESOPHAGEAL DISTRESS, COLESTID SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX COLESTID WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

PRECAUTIONS Before therapy with Colestid, a vigorous attempt should be made to control serum cholesterol with diet and weight reduction; any underlying disorder should be treated.

Colestid may interfere with normal absorption and fat, vitamins A, D, and K. Supplemental vitamins A and D should be considered.

Colestid may be associated with hypoprothrombinemia from vitamin K deficiency and can be prevented by administration of vitamin K1.

Serum cholesterol and triglyceride levels should be monitored. Colestid may raise the serum triglycerides in long-term use and, in some patients, the cholesterol levels return to baseline or rise above baseline.

Colestid may produce or severely worsen preexisting constipation. Dosage should be decreased in these patients, since impaction may occur. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with Colestid may aggravate hemorrhoids.

Use in Pregnancy and Childhood The use of Colestid in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. The safe use of Colestid resin by pregnant women has not been established. Safety and effectiveness in children have not been established.

DRUG INTERACTIONS Colestid may have a strong affinity for anions other than the bile acids. Colestid may delay or reduce the absorption of concomitant oral medication. The interval between the administration of Colestid and any other medication should be as long as possible. Patients should take other drugs at least one hour before or four hours after Colestid.

In vitro Colestid binds a number of drugs. *In vivo* studies disclosed significant effects on drug availability for L-thyroxin and aspirin, and possibly for warfarin and nicotinic acid. Decreased serum tetracycline levels were observed in a clinical study.

In preliminary studies, drug availability did not appear to be significantly altered for phenobarbital, cortisone acetate, chlorpromazine, sulfadiazine, clofibrate, and hydrochlorothiazide. Particular caution should be observed with digitalis preparations, since there are conflicting results for the effect of Colestid on the availability of digoxin and digitoxin. Discontinuing Colestid could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking Colestid.

ADVERSE REACTIONS

1. Gastrointestinal The most common adverse reactions are gastrointestinal. Constipation, one patient in 10, is the major single complaint and at times is severe and occasionally accompanied by fecal impaction. Hemorrhoids may be aggravated. Some patients require decreased dosage or discontinuation of therapy. About one in 30 to one in 100 patients reported abdominal discomfort (abdominal pain and distention), belching, flatulence, nausea, vomiting, and diarrhea. Peptic ulceration, gastrointestinal irritation and bleeding, cholecystitis, and cholelithiasis have been reported by fewer than one in 500 patients and are not necessarily drug related.

2. Hypersensitivity Urticaria and dermatitis were noted in fewer than one in 1,000 patients. Asthma and wheezing were not reported in the Colestid studies but have been noted during treatment with other cholesterol-lowering agents.

3. Musculoskeletal Muscle and joint pains and arthritis have had a reported incidence of less than one in 1,000 patients.

4. Neurologic Headache and dizziness were noted in about one in 300 patients; anxiety, vertigo, and drowsiness were reported in fewer than one in 1,000.

5. Miscellaneous Anorexia, fatigue, weakness, and shortness of breath have been seen in 1 to 3 patients in 1,000. Transient and modest elevations of serum glutamic oxaloacetic transaminase and of alkaline phosphatase were observed in various patients treated with Colestid. Some patients had increased serum phosphorus and chloride with decreased sodium and potassium.

OVERDOSE Overdosage of Colestid (colestipol hydrochloride) has not been reported. Should overdosage occur, however, the chief potential harm would be obstruction of the gastrointestinal tract.

HOW SUPPLIED Colestid (colestipol hydrochloride) is available in cartons of 30 packets and in bottles containing 500 grams of drug. Each packet or each level scoop supplies 5 grams of Colestid.

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SELF-ASSESSMENT QUIZ

The following questions are answered and discussed in recent ACCEL™ tapes.

1. Ductus arteriosus in infants can close in response to
   - A. Aspirin therapy
   - B. Indomethacin therapy
   - C. Either of the above
   - D. Neither of the above

2. Furosemide is generally not a good anti-hypertensive drug because
   - A. It is too short acting
   - B. It is too long acting
   - C. It is too toxic

3. In a series of 100 positive treadmill tests performed in apparently normal individuals, ten were ultimately shown to be falsely positive. Thus,
   - A. The sensitivity of the test is 90%
   - B. The specificity of the test is 90%
   - C. The relative statistical risk is 90%

4. Isosorbide dinitrate sublingually has been shown to decrease
   - A. After load
   - B. Pre load
   - C. Left ventricular chamber size
   - D. All of the above

ANSWERS:

1. C
2. A
3. B
4. D

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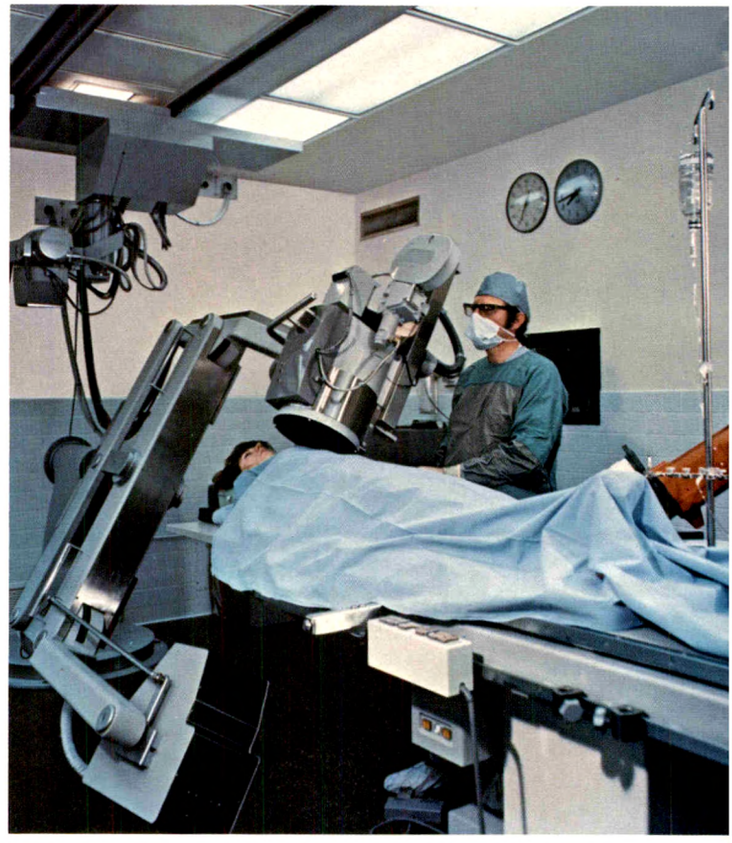


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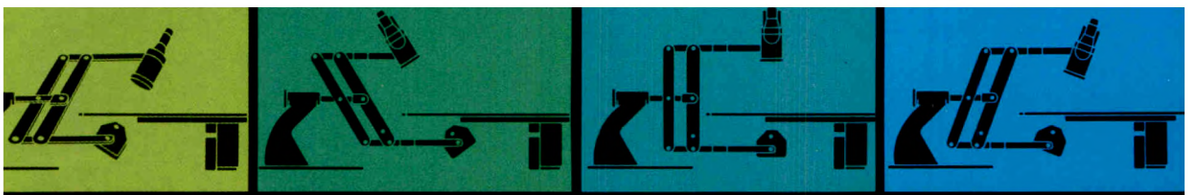
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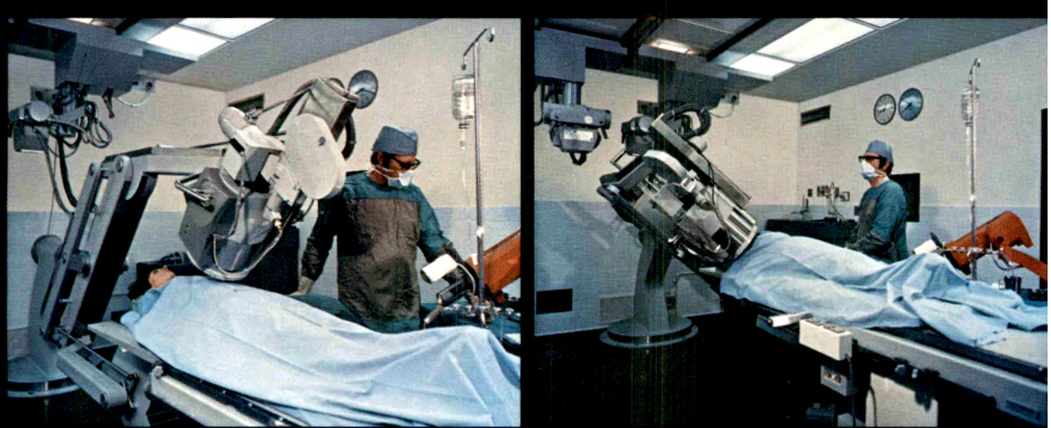
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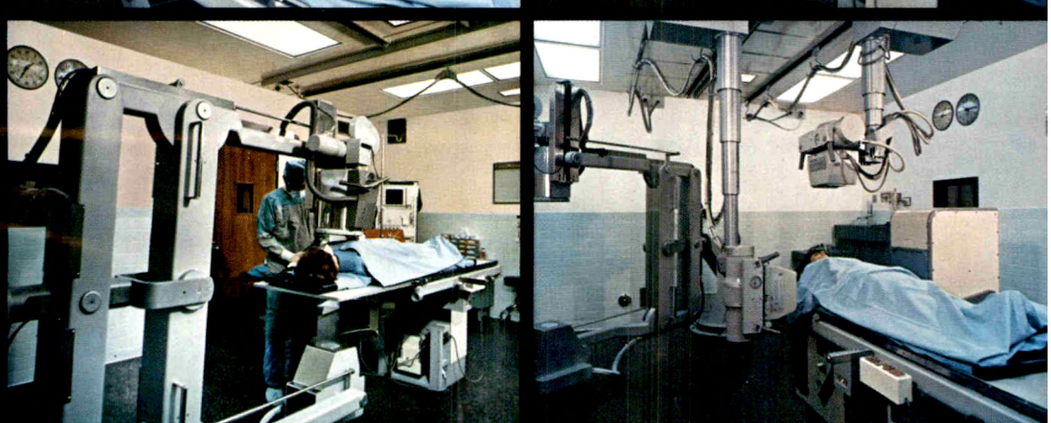


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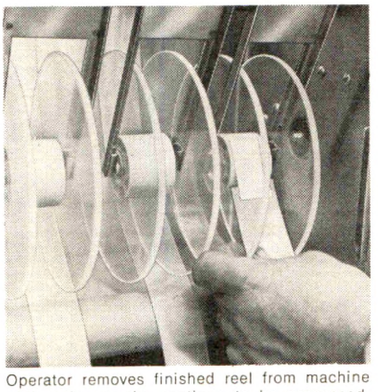
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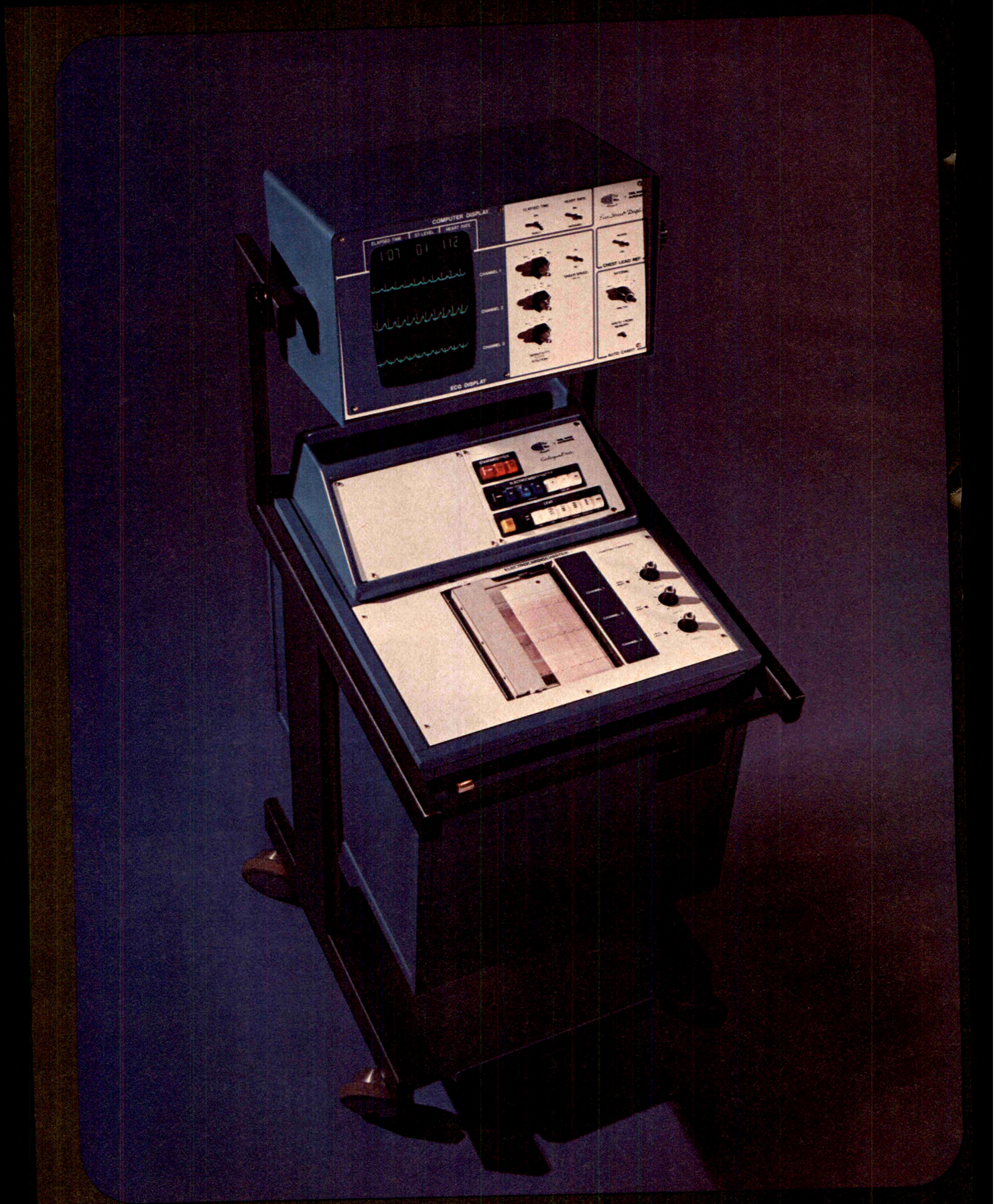
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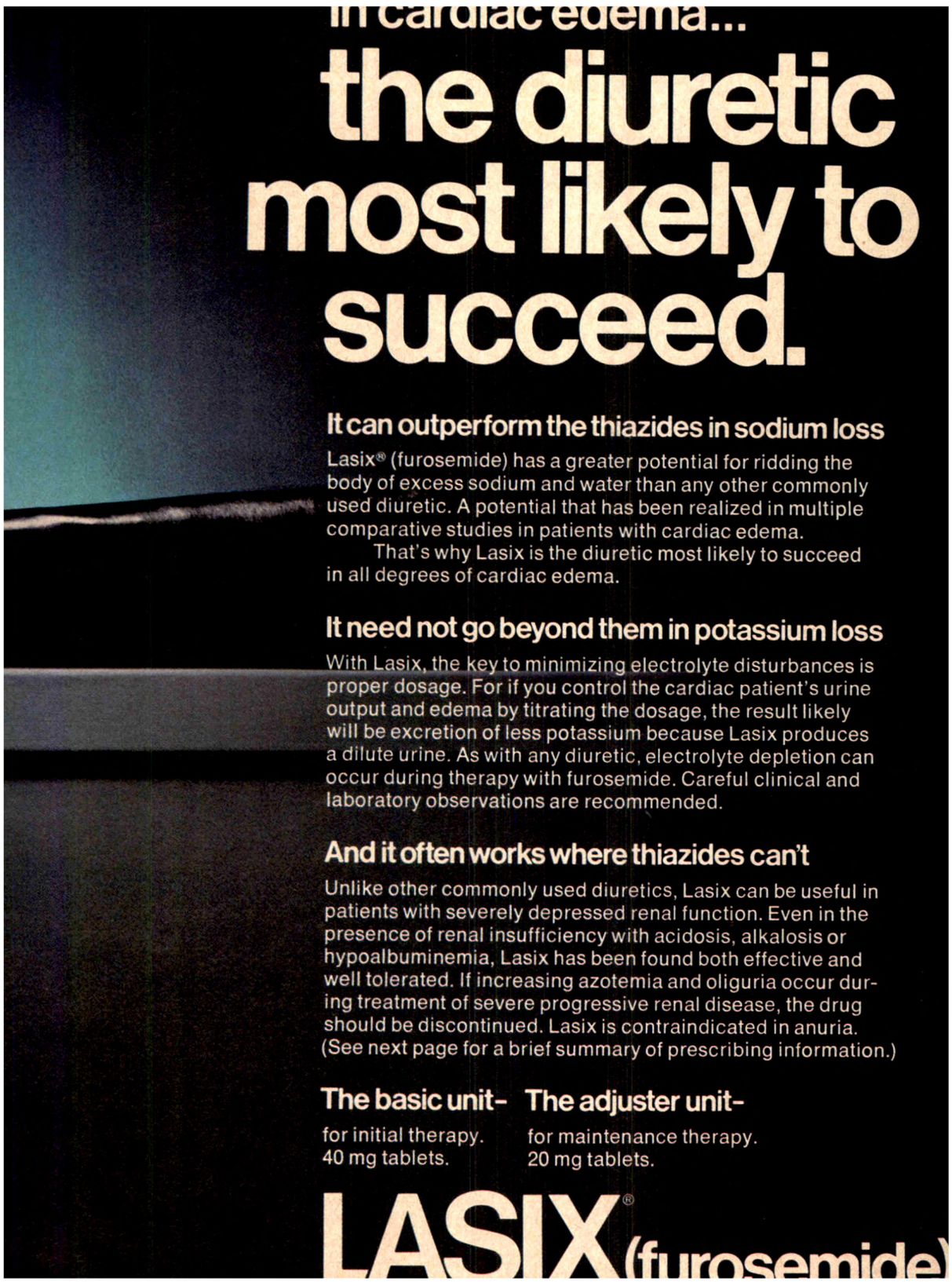
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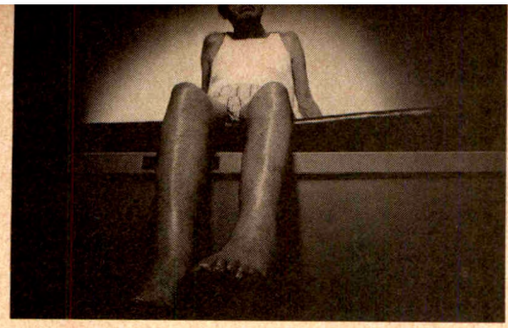
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(See next page for a brief summary of prescribing information.)
The basic unit-
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40 mg tablets.
The adjuster unit-
for maintenance therapy.
20 mg tablets.
LASIX® (furosemide)



LASIX®
(furosemide)

A brief summary of the Prescribing Information for
Lasix® (furosemide) Tablets 20 mg and 40 mg

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Hypertension—Lasix (furosemide) may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. (See "Additional Information.")

Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, an oral liquid preparation should be used rather than enteric-coated potassium salts.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix (furosemide) precedes its oral use, it should be kept in mind that cases of tinnitus and reversible hearing impairment have been reported. There have also been some reports of cases in which irreversible hearing impairment occurred. Usually, ototoxicity has been reported when Lasix (furosemide) was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were often given. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable (for adults, it has been reported that an infusion rate not exceeding 4 mg Lasix [furosemide] per minute has been used).

Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported.

Patients receiving high doses of salicylates, in conjunction with Lasix (furosemide) may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix (furosemide) and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Various forms of dermatitis, including urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli and acute pancreatitis.

Lasix (furosemide)-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Dosage and Administration

ADULTS

The usual adult dose of Lasix (furosemide) is 20 to 80 mg given as a single dose.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory, the following schedule should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. The dose of Lasix (furosemide) may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states.

With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix (furosemide) is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix (furosemide), a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix (furosemide).

INFANTS AND CHILDREN

Pediatric Administration: The usual initial dose of oral Lasix in infants and children is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg not sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

How Supplied—Lasix Tablets 40 mg (furosemide) supplied as white, round, monogrammed, scored tablets.

Lasix Tablets 20 mg (furosemide) supplied as white, oval, monogrammed tablets.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

Additional Information

Toxicology

The acute toxicity of Lasix (furosemide) has been determined in mice, rats, and dogs. In all three animal species, the oral LD_{50} of Lasix (furosemide) exceeded 1000 mg/kg of body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. Intragastric injection of the drug in newborn rats resulted in an LD_{50} of 380 mg/kg.

The acute toxicity of high doses of Lasix (furosemide) was characterized by convulsions, paralysis, and collapse. Surviving animals often became dehydrated and depleted of electrolytes due to the diuresis induced by Lasix (furosemide). In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with Lasix (furosemide) were done in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred, with all doses higher than 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day). A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg (83 percent of the maximal recommended human dose of 600 mg per day).

Reproductive Studies

The effects of Lasix (furosemide) on embryonic and fetal development and on pregnant dams were studied in mice, rats, and rabbits.

Lasix (furosemide) caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day) was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg (2 times the maximal recommended human dose of 600 mg per day) caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control group.

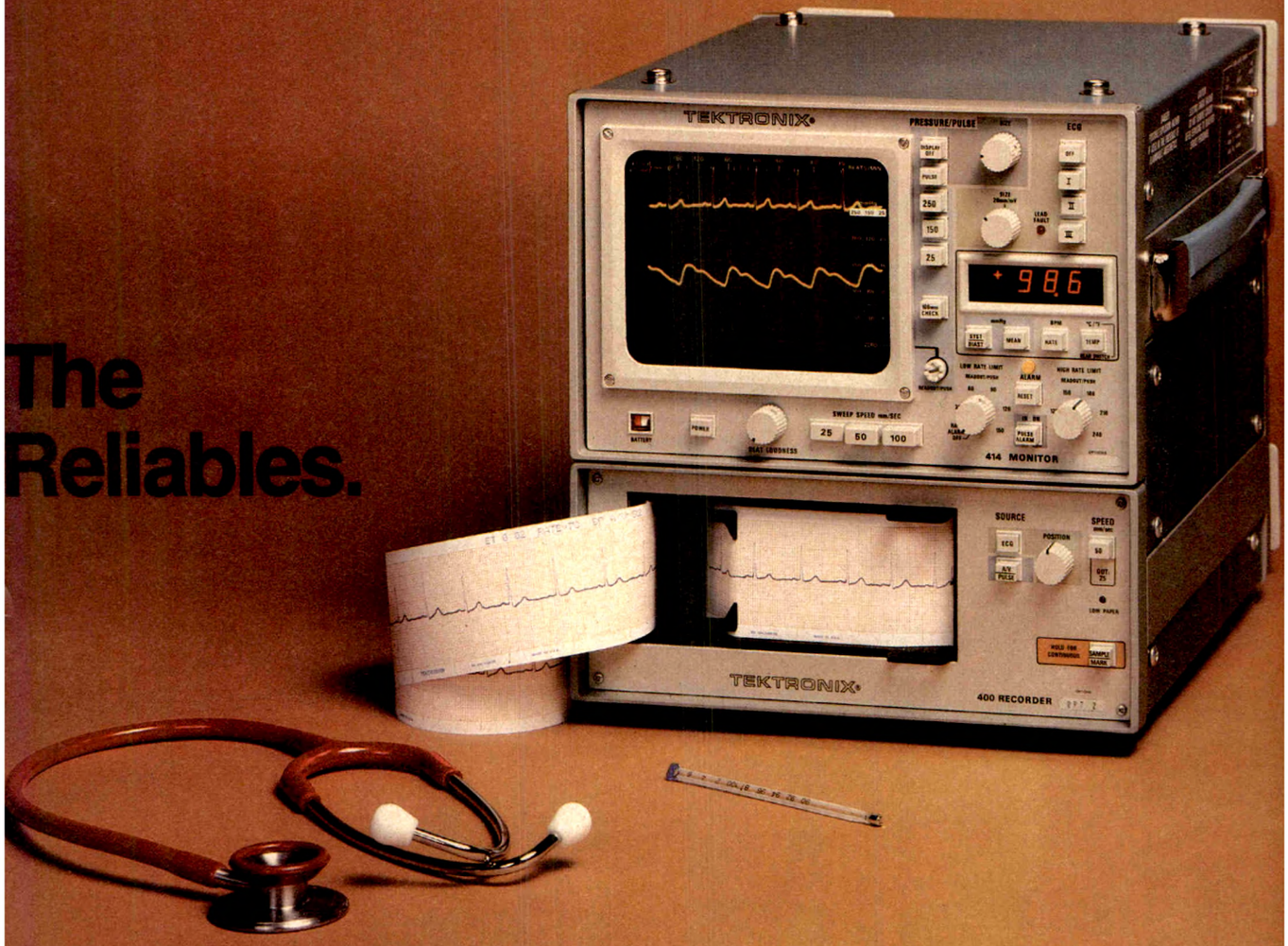
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Imaging of the Inflammatory Response in Ischemic Canine Myocardium With ^{111}Indium-Labeled Leukocytes

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MICHAEL J. WELCH, PhD
R. EDWARD COLEMAN, MD
BURTON E. SOBEL, MD, FACC

St. Louis, Missouri

Myocardial leukocyte infiltration is one hallmark of acute myocardial infarction. In order to detect noninvasively this inflammatory response associated with acute myocardial infarction, we produced coronary occlusion in eight dogs, intravenously administered autologously labeled indium-111 (^{111}In) leukocytes and scintigraphically monitored accumulation of radionuclide in myocardium. Seventy-two hours after coronary occlusion, ^{111}In-labeled white cells accumulated in regions corresponding to myocardial infarcts, and positive images with ^{111}In-labeled leukocytes correlated well with images obtained with technetium-99m pyrophosphate and computer-reconstructed tomograms obtained with nitrogen-13–labeled ammonia. In contrast, two control dogs subjected to sham operation did not exhibit positive ^{111}In-leukocyte images. Scintigraphic results with ^{111}In-labeled leukocytes were verified in vitro by analysis of radioactivity in normal myocardium and in infarcts. Thus, leukocytic infiltration associated with acute myocardial infarction can be detected noninvasively in vivo.

The inflammatory response associated with acute myocardial infarction is characterized by infiltration of polymorphonuclear leukocytes into regions with ischemic injury within 24 hours, reaching a peak within 4 to 5 days and disappearing within 2 weeks.[1–4] Activation of components of the ischemia-induced inflammatory response, such as proteases and complement,[5] have been implicated as factors potentially deleterious to ischemic myocardium.

This study was designed to develop a noninvasive technique for detecting leukocytic infiltration in vivo in the hearts of experimental animals with evolving myocardial infarction induced by coronary arterial ligation. Our approach utilized labeling of autologous leukocytes with indium-111 (^{111}In), injection of the labeled cells intravenously in eight dogs 24 hours after occlusion and performance of sequential myocardial scintigraphy up to 96 hours after occlusion. Leukocytic infiltration, detected noninvasively, was verified by analysis of blood and tissue samples obtained when the animals were killed 96 hours after coronary occlusion. In addition, several animals were evaluated noninvasively with myocardial imaging utilizing ammonia-13 and technetium-99m pyrophosphate to permit comparison with ^{111}In leukocytic scintigraphy in the same animals.

Material and Methods

Preparation of labeled leukocytes: *Autologous labeled leukocytes were obtained as follows:* 40 ml of venous blood from each dog was drawn into a 50 ml syringe containing 1,000 U of preservative-free sodium heparin. After the blood was transferred into a sterile glass tube, 3 percent (volume/volume) methyl cellulose solution (2 percent methyl cellulose in normal saline solution [weight/volume]) was added. After gentle mixing and sedimentation for 1 hour, the leukocytes were harvested from the leukocyte-rich plasma by centrifugation

From the Washington University School of Medicine, St. Louis, Missouri. This work was supported in part by Grants HL 17646, SCOR in Ischemic Heart Disease and HL 14147, SCOR in Thrombosis from the National Institutes of Health, Bethesda, Maryland. Manuscript received November 5, 1976; revised manuscript received February 7, 1977, accepted February 9, 1977.

Address for reprints: Burton E. Sobel, MD, Cardiovascular Division, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110.

at 450 *g* for 5 minutes and two washes with normal saline solution. Under these conditions, approximately 80 percent of leukocytes are recovered with less than 5 percent contamination with erythrocytes.[6]

Among several radioisotopes utilized to label leukocytes, ^{111}In is particularly suitable.[7] This radionuclide emits gamma photons (173 kev, 247 kev) readily detectable with conventional imaging devices. It has a half-life of 67 hours, permitting imaging during an interval of several days after a single injection without administration of large amounts of radioactivity. On the basis of preliminary studies with several compounds, the ^{111}In complex of 8-hydroxyquinoline was utilized.[8]

Indium-111 chloride solution (Medi-Physics) was chelated with 8-hydroxyquinoline at pH 5.0 as follows: 1.5 ml of ^{111}In chloride solution was added to an equal volume of water, 200 μl of 0.3 molar acetate buffer, pH 5.0 and 150 μl of 8-hydroxyquinoline, 1 mg/ml, in ethanol. After the complex was extracted in an equal volume of chloroform, the solvent was evaporated. The complex was resuspended in 100 μl of ethanol and diluted to 500 μl with normal saline solution. This solution was added by drops to a suspension of leukocytes recovered from 40 ml of blood and suspended in 5 ml of normal saline solution. The mixture was incubated at room temperature for 25 minutes and centrifuged at 450 *g* for 5 minutes. Under these conditions 75 to 95 percent of the radioactivity was incorporated by the cells. Free ^{111}In was removed from the cells by repeated washing in saline solution until the supernatant fraction exhibited no activity. The labeled cells were then suspended in 2 ml of normal saline solution to break up clumps and diluted with 4 ml of plasma before intravenous administration to each dog. This preparation contained no detectable ^{111}In in cell free fractions.

Animal preparations: Ten animals were anesthetized with sodium pentobarbital (30 mg/kg intravenously). Blood was withdrawn from each dog for the preparation of autologous labeled leukocytes. Ventilation was maintained with room air with the use of a Harvard pump. The electrocardiogram was monitored and recorded at 30 minute intervals. One of several surgical procedures was used, including left thoracotomy with no coronary occlusion (sham operation), coronary occlusion in open chest animals with left or right thoracotomy and coronary occlusion induced by constriction of an exteriorized snare 1 week after thoracotomy in closed chest dogs. After sham operation or coronary occlusion, each animal was studied with serial images obtained after intravenous injection of ^{111}In-labeled leukocytes beginning 24 hours after coronary occlusion and at corresponding times in control animals. After imaging, each animal was killed with an overdose of sodium pentobarbital. Blood samples and samples of normal and ischemic myocardium were analyzed for ^{111}In radioactivity.

Eight animals were subjected to coronary occlusion. The coronary artery was exposed and separated from the adjacent vein approximately 0.5 cm distal to its point of emergence from beneath the left atrial appendage. In acute experiments, the vessel was occluded with an O silk suture. In other experiments the vessel was occluded 1 week after operation by constriction of an exteriorized snare placed around the artery. Lidocaine, 3 mg/kg intravenously, was administered immediately before coronary occlusion to reduce the incidence of malignant ventricular arrhythmia.

Two animals were subjected to sham operation (left thoracotomy and coronary dissection without coronary occlusion) to permit evaluation of the extent to which incisional leukocytic infiltration contributed to positive images. Four dogs were subjected to occlusion of the left anterior descending coronary artery with use of a left or right thoracotomy at the time of operation. The right thoracotomy was performed in two animals to avoid subsequent superimposition in the myocardial scintigram from leukocytic infiltration within the thoracotomy incision overlying a region of infarction. Four dogs had exteriorized O silk coronary snares placed around the left anterior descending artery through a left thoracotomy. These animals were permitted to recover for 1 week and then underwent imaging 12 hours before and again up to 96 hours after coronary occlusion induced by constriction of the snare. This procedure was utilized to differentiate a positive image resulting from incisional leukocytic infiltration from one due to myocardial leukocytic infiltration induced by ischemia.

Scintigraphy and detection of radioactivity in the heart in vitro: Twenty-four hours after operation ^{111}In-labeled autologous leukocytes (2 mCi, approximately 3×10^8 cells) were injected intravenously in each dog, and cardiac images were obtained serially for 96 hours. From 12 to 24 hours after the injection of ^{111}In, each dog was again anesthetized with sodium pentobarbital, and anterior, oblique and left lateral images were obtained with a scintillation camera equipped with a high resolution collimator. Imaging was performed in a similar fashion at 12 hour intervals for 96 hours.

Additional images were obtained in two dogs 48 hours after coronary occlusion after administration of 3 mCi of technetium-99m stannous (^{99m}Tc[Sn]) pyrophosphate and 4 mCi of ammonia-13 ($^{13}NH_3$). These animals were studied in anterior, oblique and left lateral projections for detection of myocardial infarction scintigraphically with pyrophosphate[9] and with use of positron emission transaxial tomography.[10]

Ninety-six hours after administration of ^{111}In-leukocytes, each dog was killed with intravenously administered sodium pentobarbital. The chest was opened through the same incision used for the initial operation and the heart was removed rapidly. The presence of myocardial infarction was verified with gross examination and histologic studies.

At least two sections of myocardium were obtained for assessment of radioactivity: one, a 1 cm thick section from a region 2 cm distal to the coronary occlusion, and the other (control), a section from the posterior wall of the left ventricle at the same level. Blood samples, 5 ml, were also obtained. All samples were weighed and counted with fixed geometry with the use of a 3 inch (7.6 cm) NaI detector.

Results

No dense scintigraphic accumulation of ^{111}In-labeled white cells was noted during the entire 96 hour interval in the control animals subjected to sham operation. One control animal had a minimally detectable linear streak corresponding to the site of the incision.

Scintigrams in myocardial infarction: In animals with coronary occlusion and right thoracotomy, the ^{111}In leukocyte image obtained 48 hours after coronary occlusion corresponded to a region of infarction and not to the site of the incision (a potential source for false positive images with the labeled leukocyte technique), which was on the opposite side of the thorax.

Positive scintigrams of myocardial infarction obtained with ^{111}In-labeled leukocytes after left thoracotomy were concordant with those obtained with ^{99m}Tc(Sn) pyrophosphate (Fig. 1). ^{111}In radioactivity detected in the region of infarction produced with this

model was most prominent 48 hours after coronary occlusion in the studies with labeled leukocytes. In addition, as shown in Figure 1, $^{13}NH_3$ perfusion imaging assessed with use of reconstruction positron emission tomograms in these animals defined a hypoperfused zone that correlated closely with infarction detected by both the ^{111}In leukocyte and ^{99m}Tc pyrophosphate.

Scintigraphically, the right and left lobes of the liver were consistently visualized in all animals. Hepatic accumulation of ^{111}In leukocyte preceded myocardial accumulation in animals subjected to coronary occlusion.

In animals with exteriorized snares around the left anterior descending coronary artery, ^{111}In images obtained before coronary occlusion were negative or showed only linear accumulation of isotope corresponding to the site of the incision. However, 72 hours after constriction of a coronary snare in the same dogs, positive scintigrams were obtained.

Radioactivity in myocardium: Animals with coronary occlusion exhibited an 11.4 ± 5.0 (mean ± standard error of the mean) fold excess ^{111}In radioactivity in zones of infarction analyzed in vitro compared with nonischemic myocardium (no. = 8 samples from 6 hearts). Between 0.008 and 0.015 percent of counts in the injectate were recovered per gram of myocardial infarct compared with 0.0002 percent of counts per gram of blood. The observed ratios of radioactivity in infarct and in normal myocardium were comparable in animals with left and right thoracotomy. Counts from the anterior portions of hearts of control animals undergoing sham operation were significantly lower than those in corresponding regions undergoing infarction in hearts from animals with coronary occlusion. On the other hand, counts from anterior and posterior portions of the hearts of control animals were similar to each other and virtually identical to those seen in normal myocardium from hearts of animals with coronary occlusion.

Myocardial infarction was verified with gross inspection and histologic study in all animals with coronary occlusion. All areas of infarction contained abundant leukocytes, particularly in the peripheral zones (Fig. 2).

Discussion

In this study, autologous ^{111}In-labeled leukocytes were utilized for external, noninvasive detection of the

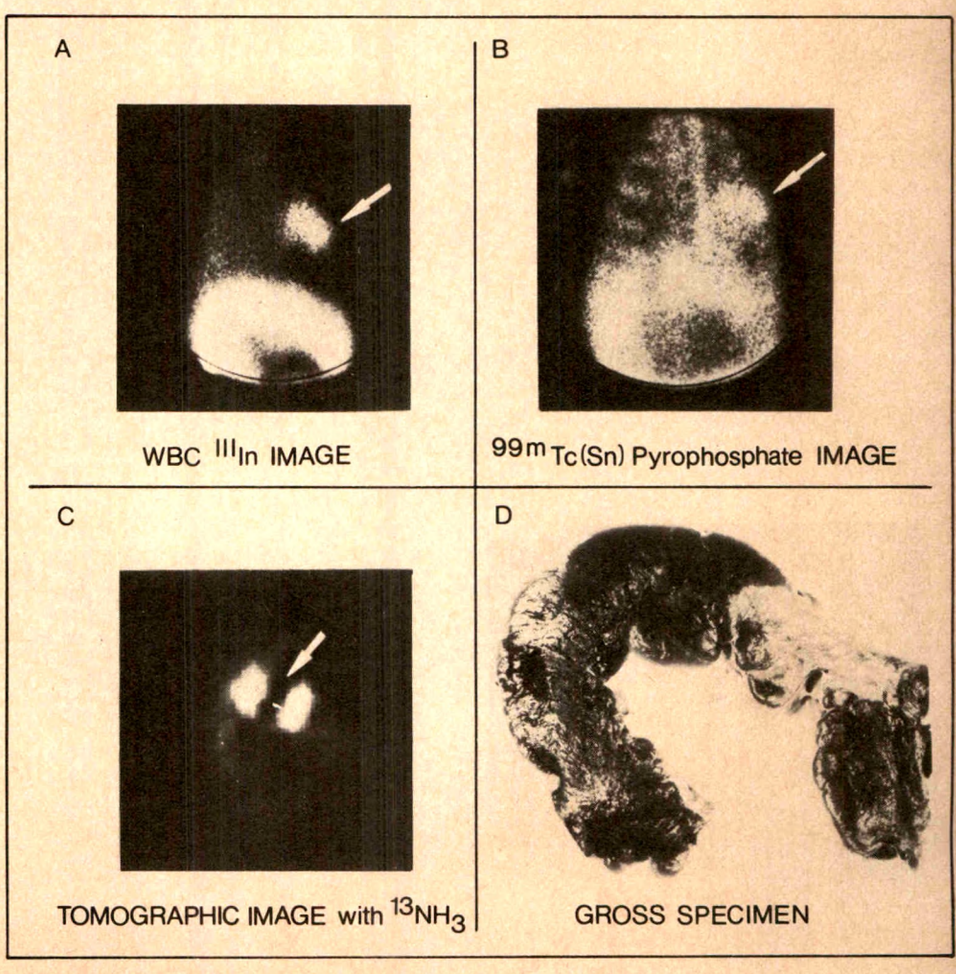


FIGURE 1. The four panels depict results from the same canine heart. **A,** scintigram obtained 72 hours after coronary occlusion after injection of indium-111-(^{111}In)-labeled leukocytes (WBC). Accumulation of labeled leukocytes in the infarct is evident **(arrow)** and corresponds to accumulation of technetium-99m stannous (^{99m}Tc[Sn]) pyrophosphate detected scintigraphically **(arrow)** after intravenous injection of the radiopharmaceutical at the same time **(B)**. Both ^{111}In and ^{99m}Tc(Sn) pyrophosphate accumulate in the liver, but ^{111}In-labeled leukocytes do not image ribs and spleen under these conditions in contrast to ^{99m}Tc(Sn) pyrophosphate. **C,** positron emission transaxial tomogram obtained with ammonia-13 ($^{13}NH_3$) perfusion imaging, depicting a 1.5 cm thick cross section of the heart at the level of the atrioventricular valves.[11] The posterior border is not visualized because it comprises left atrium. Anteriorly, a transmural perfusion defect is evident **(arrow)** corresponding to the locus of infarction shown in the photograph of the same cross section (depicted as a light region in **D).**

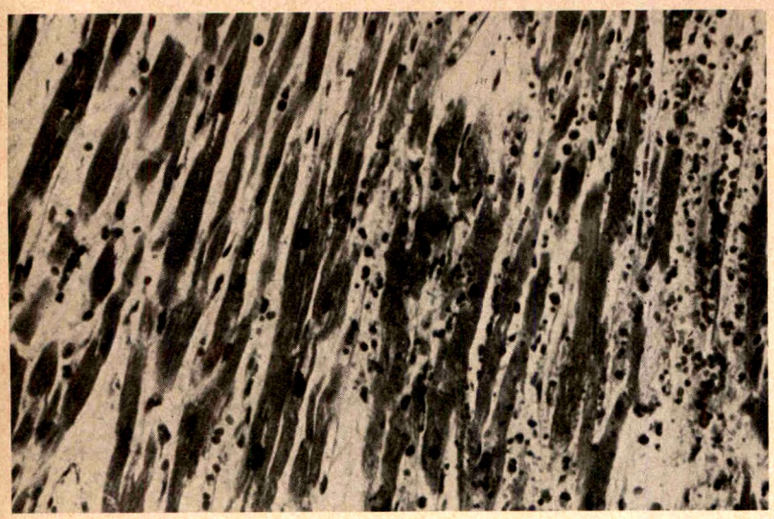


FIGURE 2. Photomicrograph of myocardium confirming leukocytic infiltration 50 hours after coronary occlusion in an animal with a positive scintigram after intravenous injection of ^{111}In-labeled leukocytes (hematoxylin-eosin ×250, reduced by 10 percent.)

inflammatory response associated with myocardial infarction manifested by leukocytic infiltration. The inflammatory changes associated with acute myocardial infarction have been characterized in studies requiring tissue samples, generally obtained at necropsy.[2,4] As early as 1899,[3] leukocytic infiltration was observed beginning 3 days after the onset of acute myocardial infarction. Subsequently, in studies of experimental myocardial infarction in dogs, Karsner and Dwyer[4] found that infiltration of polymorphonuclear leukocytes began as early as 12 hours after coronary occlusion, increased substantially within 24 hours and constituted a marginating zone defining the periphery of an infarct within 5 days. Polymorphonuclear leukocytes as well as lymphocytic infiltration persisted for as long as 18 days, but cell infiltration was invariably absent after 61 days.

In patients who die with acute myocardial infarction, polymorphonuclear infiltration in the periphery is apparent within 24 hours. It invariably accompanies necrosis.[2] Infiltration is most prominent in regions of necrotic tissue adjacent to normal myocardium with intact vasculature. It is maximal after 3 to 4 days, decreases during the ensuing 14 days and generally disappears within 2 weeks after the onset of infarction.

Despite the prominence of leukocytic infiltration and the possibility that inflammation may greatly influence the evolution of infarction,[5,12] it has not previously been possible to detect myocardial leukocytic infiltration serially in vivo. Labeling of leukocytes with ^{111}In appears to be a useful technique permitting sequential detection of leukocytic infiltration in experimentally induced abscesses and scintigraphic detection of inflammation secondary to infection in patients.[13,14] ^{111}In emits two gamma photons of 173 kev and 247 kev suitable for external detection with either a gamma camera or a rectilinear scanner. The half-life of the radionuclide (67 hours) permits sequential studies for several days, without excessive radiation burden.

Clinical applications: Several conditions in addition to myocardial infarction may be amenable to evaluation with the technique of ^{111}In-leukocytic scintigraphy. For example, it is possible that leukocytic infiltration associated with bacterial endocarditis or myocarditis could be recognized with the use of ^{111}In-labeled white cells and that myocarditis could be differentiated from noninflammatory cardiomyopathy on this basis. In addition, pericarditis, particularly with associated epicarditis, might be detectable on the basis of leukocytic infiltration in those episodes characterized by an extensive inflammatory response. Definitive studies will be required to determine whether the technique described is applicable to these entities, but the positive results evident in analysis of hearts undergoing ischemic injury suggest that leukocytic infiltration will be detectable in other conditions as well.

The technique described in this study should be applicable to patients as well as to experimental animals because of the relatively small dose of radioactivity required in injectates and the short half-life (2.8 days) of ^{111}In. The radiation burden is small, and the technique is noninvasive.

Our results in this study indicate that leukocytic infiltration associated with acute myocardial infarction can be detected serially and noninvasively. The technique employed provides a potentially useful addition to the scintigraphic assessment of ischemic myocardial injury manifested by a characteristic inflammatory response. Utilization of ^{111}In leukocytic scintigraphy with other noninvasive methods of delineating perfusion abnormalities and necrotic myocardium may permit a more complete characterization of the evolution of ischemic injury and its response to potentially therapeutic interventions.

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Relation Between Progressive Decreases in Regional Coronary Perfusion and Contractile Abnormalities

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To determine the quantitative relation between partial coronary obstruction and its resultant effects on local contraction, the left anterior descending coronary artery was partially obstructed (while the decrease in both distal pressure and flow were observed) and local tension and length were measured in 10 open chest dogs. A pressure gradient index ([AO-COR] /AO) across the obstruction was derived, where AO = mean aortic pressure and COR = mean distal coronary pressure, and was correlated with change in flow (control flow = 95.3 ± 3.8 ml/100 g). Contractile function of ischemic and nonischemic zones was measured using both Walton-Brodie strain and mercury-in-Silastic segment length gauges. Small pressure gradients (index 0.27 ± 0.03 [mean ± standard error of the mean]) and decreases in distal flow (to 74.2 ± 1.6 ml/100 g) caused no change in tension or length. Further reduction in distal pressure (gradient index 0.52 ± 0.04) and flow (to 50.0 ± 0.8 ml/100 g) produced a decrease in tension to 87.3 ± 3.6 percent of control level ($P < 0.005$) and an increase in length to 129.1 ± 4.6 percent ($P < 0.01$). The upstroke of the tension curve during the ejection phase persisted despite the decrease in total tension. Additional reduction of pressure (gradient index 0.71 ± 0.03) and flow (27.7 ± 1.3 ml/100 g) caused a marked decrease in tension to 55.5 ± 11.9 percent of control level ($P < 0.01$) and an increase in length to 182.0 ± 14.1 percent ($P < 0.001$). The tension curve demonstrated loss of ejection tension with a negative slope inscribed during the ejection phase. Total occlusion resulted in no additional decrease in distal pressure and, although flow decreased to 5.0 ± 1.2 ml/100 g, no further change in tension (56.8 ± 9.3 percent) or length (183.3 ± 8.9 percent) occurred.

Thus, an acute reduction in coronary pressure and flow of 50 percent or more results in regional contraction abnormalities that are further accentuated as the pressure and flow are reduced by 75 percent or more. Maximal abnormalities produced by total occlusion are similar to those produced by a reduction in flow of 75 percent or more.

Since the classic study of Tennant and Wiggers[1] in 1935 it has been known that complete coronary occlusion results in severe regional contraction abnormalities manifested as paradoxical systolic expansion. More recently, experimental studies[2–5] have indicated that complete coronary occlusion produces an immediate and substantial decrease in local tension and an increase in segment length of both the central ischemic and border zones. Clinically, coronary arteriographic and ventriculographic studies[6,7] have clearly demonstrated that lesser degrees of coronary obstruction are also frequently associated with local contraction abnormalities. Recent studies by Wyatt et al.[8] indicate that there is only minimal reduction in the area of the pressure-length loop until flow and pressure are critically reduced at which time a sharp decrease in regional function becomes apparent. The coronary arteries in their studies were cannulated, and pressure and flow regulated using a

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perfusion pump. This experimental study was therefore undertaken to evaluate the quantitative relation between partial obstruction of the native coronary arteries and the resultant effects of graded decreases in coronary pressure and flow on regional left ventricular contraction.

Methods

Instrumentation: Experiments were performed in 11 dogs weighing 23 to 27 kg, anesthetized with sodium pentobarbital (30 mg/kg intravenously). The animals were ventilated with an endotracheal tube connected to a Harvard respirator. A polyethylene tube was introduced through an external jugular vein for intravenous infusion. A stiff bore catheter was introduced into the ascending aorta by way of a femoral artery for monitoring central aortic pressures. A specially designed no. 8F angiographic catheter was fluoroscopically positioned at the ostium of the left coronary artery through a right carotid arteriotomy. A no. 3F radioopaque catheter was advanced through the lumen of the angiographic catheter and positioned in either the left anterior descending or the left circumflex coronary artery. The angiographic catheter was then removed from the coronary arterial ostium. The intracoronary catheter was kept flushed with heparinized saline solution (0.3 cc/min) using an infusion pump.

The heart was exposed through a thoracotomy in the fourth intercostal space in the left lateral position and supported in a pericardial cradle. A 2 cm long segment of the left anterior descending or circumflex artery (whichever vessel contained the intracoronary catheter) was exposed and mobilized. An umbilical tape was passed around the coronary artery proximal to the tip of the intracoronary catheter and was utilized as a snare for producing graded coronary occlusions. An electromagnetic flow probe (Micron MU 1001-B) was then placed on the coronary artery distal to the tip of the intracoronary catheter for monitoring coronary flow below the occlusion. The electromagnetic flow probe was initially calibrated electronically to obtain a zero baseline in normal saline solution. At the end of each experiment, the mobilized segment of the coronary artery was transected and cannulated with a large bore (generally no. 6F) polyethylene tube. The calibration of the flow probe was then confirmed by pumping known rates of blood flow infused through the artery using a Harvard infusion pump. Two Walton-Brodie strain gauge arches were placed with deep sutures at 30 to 40 percent stretch, one in the potentially ischemic and one in the nonischemic zone.[2,3] A mercury-in-Silastic® segment length gauge was also sutured adjacent and parallel to the strain gauge arch in each zone.[2,3] The method utilized to document the ischemic zone accurately has previously been described in detail.[2,3] In brief, the central ischemic zone was delineated by determining the zone in which epicardial S-T segment elevation was recorded during transient occlusion of the coronary artery. At least 10 minutes was allowed for the S-T segments to return to baseline after release of the occlusion. The strain and length gauges were then sutured in the central area where maximal S-T elevation was observed during transient occlusion.

Graded decreases in coronary pressure and flow: During each experiment, graded coronary occlusion was produced by gradually tightening the snare around the coronary artery. The degree of occlusion was quantitated by monitoring both flow (using an electromagnetic flow probe) and distal coronary pressure. Measurements were obtained during occlusion approximating 25, 50 and 75 percent decreases from the control level of flow. These decreases in coronary flow correlated closely with the decreases in mean distal coronary pressure (Fig. 1).

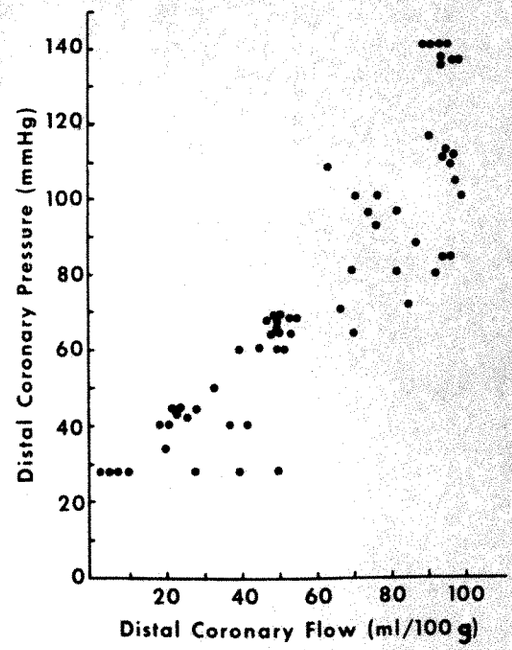


FIGURE 1. Correlation of distal coronary pressure and flow (r = 0.908).

At the end of each experiment, 2 cc of methylene blue was injected at systemic pressure into the distal coronary segment and the myocardium subserved by this segment was resected and weighed. Coronary flow data obtained from the electromagnetic flow probe were then recalculated according to the weight of the muscle obtained and expressed as ml/100 g. A pressure gradient index ($[\overline{AO}\text{-}\overline{COR}]/\overline{AO}$, where $\overline{AO}$ = mean aortic pressure and $\overline{COR}$ = mean distal coronary pressure) that closely approximated the decrease in flow distal to the obstruction was derived (see Results). The pressure gradient index thus reflected the mean gradient across the coronary obstruction, that is, the pressure distal to the obstruction corrected for aortic pressure. A low pressure gradient index was associated with greater distal flow (thus indicating a less severe obstruction) and a higher pressure gradient index corresponded to lesser distal flow (thus indicating a more severe obstruction).

The following variables were measured as percent change from control as an index of contractile performance of the ischemic and the nonischemic myocardium: (1) total tension, (2) rate of tension rise (dT/dt), and (3) segment length.[2,3] Each degree of coronary occlusion was maintained for 5 minutes, and continuous recordings of changes in segment tension and length were made on an Electronics for Medicine DR8 oscilloscopic recorder. A 5 minute period of coronary occlusion was chosen because our previous studies on total coronary occlusion[2,3] indicated that the effects of occlusion on measures of myocardial contractility generally became stable within this time period and were completely reversible if the occlusion was released. This procedure allowed multiple observations in the same experimental animal for confirming the reproducibility of these observations. After release of the occlusion, at least 30 minutes was allowed for the coronary flow, tension and length to return to control values. Distal coronary pressure, flow, tension and length data were measured and analyzed at the end of the 5 minute occlusion period. Statistical analysis was performed by Student's t test for paired values.

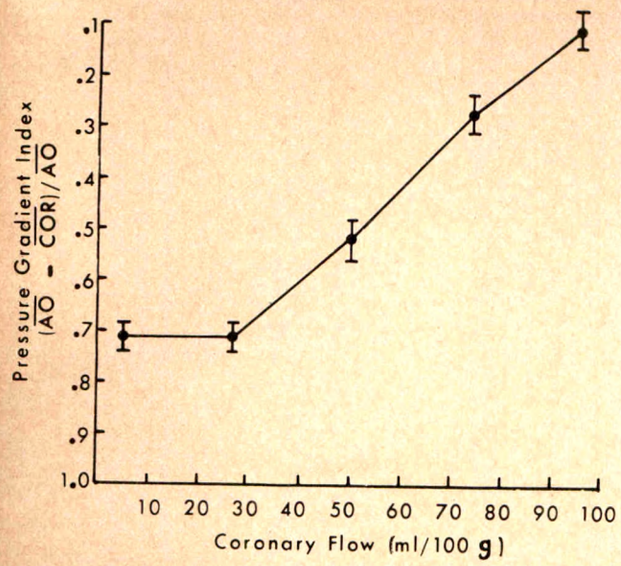


FIGURE 2. Correlation of distal coronary flow and pressure gradient across the partial coronary obstruction. AO = mean aortic pressure; COR = mean coronary pressure below the obstruction.

Results

Correlation of decrease in pressure with decrease in distal coronary flow: Figure 1 demonstrates the correlation of distal coronary pressure with distal coronary flow as the coronary occlusion was gradually increased. An excellent linear correlation existed between the decrease in pressure and the decrease in flow ($r = 0.908$).

The correlation between distal coronary flow and pressure gradient across the partial obstruction is demonstrated in Figure 2. The mean control flow in these experiments was 95.3 ± 3.8 ml/100 g (mean ± standard error of the mean). A small reduction in coronary pressure and a correspondingly low pressure gradient index of 0.27 ± 0.03 resulted in a mean distal flow of 74.2 ± 1.6 ml/100 g. Increasing the pressure gradient index to 0.52 ± 0.04 reduced distal flow to 50.0 ± 0.8 ml/100 g. Further reduction of distal coronary pressure increasing the gradient index to 0.71 ± 0.03 corresponded to a reduction in flow to 27.7 ± 1.3 ml/100 g. Total coronary occlusion caused no further change in the pressure gradient index but coronary flow decreased to 5.0 ± 1.2 ml/100 g.

Effect of graded coronary occlusion on contractile performance in the ischemic zone: A typical experiment showing the effect of graded coronary occlusion on tension development in the ischemic zone is shown in Figure 3, which illustrates simultaneous changes in distal coronary pressure, flow and segment tension. In the control panel, when the distal coronary flow is normal and the mean distal coronary pressure equals mean aortic pressure (superimposed), the resultant preejection and ejection contour of the tension curve is normal. No change in the tension curve is observed with 25 percent reduction in distal coronary flow and pressure. When distal coronary flow and pressure are reduced to approximately 50 percent of control level, there is a significant decrease in preejection and total tension although the ejection phase of the tension curve is maintained at a reduced level. With reduction in flow and pressure to approximately 75 percent obstruction,

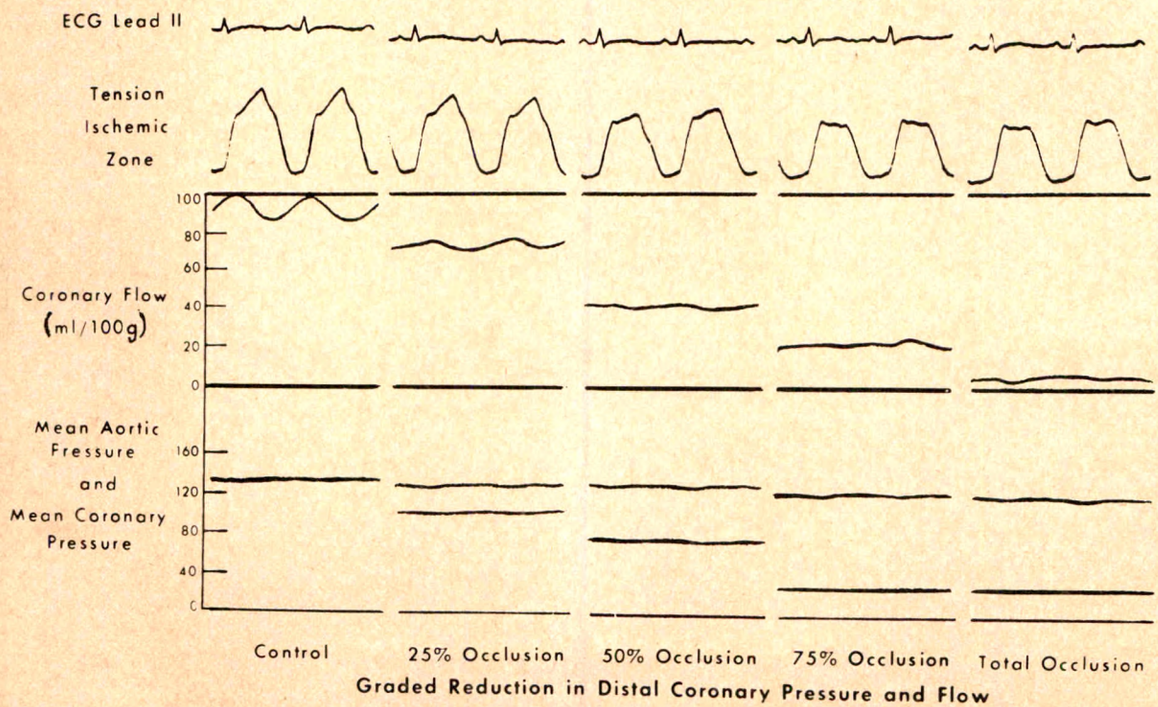


FIGURE 3. Typical experiment demonstrating the effect of graded coronary occlusion on tension development in the ischemic zone (see text). ECG = electrocardiogram.

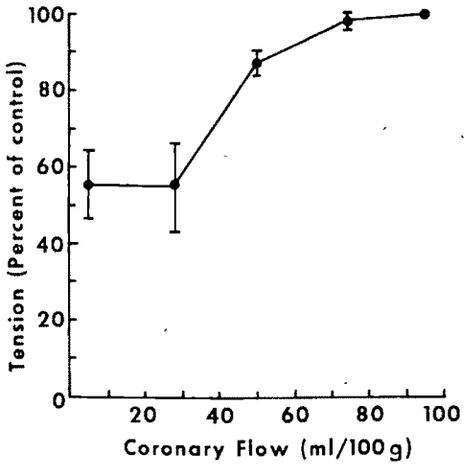


FIGURE 4. Effect of graded coronary occlusion on ischemic zone tension (see text).

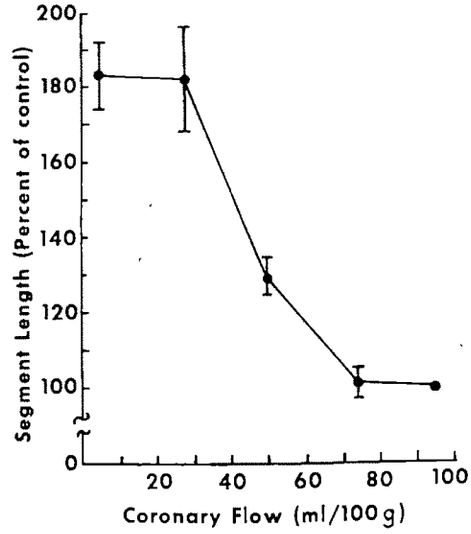


FIGURE 5. Effect of graded coronary occlusion on ischemic zone segment length (see text).

preejection tension decreases further and a negative tension slope is observed in the ejection phase. Total coronary occlusion, which causes further reduction in flow but no change in distal coronary pressure, results in no significant further decrease in tension.

Total tension: Figure 4 shows the quantitative effect of graded decreases in coronary blood flow on total tension in the ischemic zone. When coronary flow was decreased to 74.2 ± 1.6 ml/100 g (at a pressure gradient index of 0.27 ± 0.03), there was no significant change in total tension. However, reduction of coronary flow to 50.0 ± 0.8 ml/100 g (with a pressure gradient index of 0.52 ± 0.04) significantly decreased tension to 87.3 ± 3.6 percent of control level (P <0.005). When distal coronary flow was further reduced to 27.7 ± 1.3 ml/100 g (the pressure gradient index being 0.71 ± 0.03), a further decrease in tension to 55.5 ± 11.9 percent of control level (P <0.01) occurred. However, total coronary occlusion (coronary flow 5.0 ± 1.2 ml/100 g) caused no further change in total tension (56.8 ± 9.3 percent).

Rate of rise in tension (dT/dt): This rate showed changes parallel to those of total tension. A coronary flow level of 74.2 ± 1.6 ml/100 g did not significantly change dT/dt. However, a reduction in coronary flow to 50.0 ± 0.8 ml/100 g significantly decreased dT/dt to 83.0 ± 7.3 percent of control level (P <0.01). When coronary flow was reduced to 27.7 ± 1.3 ml/100 g (pressure gradient index of 0.71 ± 0.03), a further decrease in dT/dt to 58.3 ± 8.8 percent of control level (P <0.005) occurred. Total coronary occlusion caused no further changes in dT/dt (54.5 ± 6.9 percent of control level).

Segment length: The effect of graded reduction in distal coronary flow on segment length is shown in Figure 5. At a coronary flow rate of 74.2 ± 1.6 ml/100 g, no significant change in segment length was observed. When flow was reduced to 50.5 ± 0.8 ml/100 g, segment length increased to 129.1 ± 4.6 percent of control level (P <0.01). Further reduction of flow to 27.7 ± 1.3 ml/100 g caused a further increase in segment length to 182.0 ± 14.1 percent of control level (P <0.001). Total coronary occlusion (coronary flow 5.0 ± 1.2 ml/100 g) caused no further change in segment length (183.3 ± 8.9 percent of control level).

Effect of graded coronary occlusion on the nonischemic zone: The nonischemic zone showed no significant changes in segment tension or length with the graded coronary occlusions.

Discussion

Experimental studies have demonstrated that myocardial revascularization after acute coronary ligation is of little benefit in the preservation of myocardium as ascertained with contractile, biochemical or electrographic variables.[3,9–11] However, these data are somewhat difficult to extrapolate to the setting of acute ischemic injury in man which, in contrast to animal studies, is frequently associated with angiographic and pathologic evidence of partial coronary occlusion.[6,7,12] In addition, the experimental assessment of the value of pharmacologic interventions in acute ischemia has largely been performed after total coronary occlusion, and the value of such interventions in partial coronary occlusion has received only preliminary assessment.[8,13,14] Thus, an understanding of the effect of various degrees of partial coronary occlusion on zonal contraction should serve as a useful baseline for assessment of such interventions.

Relation between contractile function and diminished coronary flow: This study demonstrates that coronary obstruction resulting in approximately a 25 percent reduction in distal pressure and flow causes no abnormalities in segmental function. However, a further reduction in distal coronary pressure and flow to 50 percent of control level results in significant regional dysfunction manifested by a reduction in total tension development and an increase in segment length (Fig. 4 and 5). However, regional myocardial shortening persists throughout systole, although at a decreased

level, because tension is maintained during the ejection phase (Fig. 3). When a 75 percent decrease in coronary pressure and flow is produced, there is a further accentuation of abnormalities in both tension and length (Fig. 4 and 5). In addition, systolic fiber shortening disappears and there is paradoxical systolic expansion manifested by loss of tension during the ejection phase (Fig. 3). Although total coronary occlusion in these short-term studies produced a further decrease in coronary blood flow, no additional short-term abnormalities in contraction were observed (Fig. 3). Thus, the relation between the decreases in regional coronary flow and resultant contraction abnormalities resembles a sigmoid curve, and the loss of contractile ability appears to take place over a relatively short portion of the progressively decreasing coronary pressure-flow curve (Fig. 4 and 5). These findings are consistent with those of Wyatt et al. and Daniell.[8,15] However, in both of these studies, the coronary artery was cannulated and perfusion controlled with use of a perfusion pump. Wyatt et al.[8] produced graded reductions in regional coronary perfusion and observed that regional function decreased minimally as coronary perfusion pressure and flow were reduced to 50 to 60 mm Hg and 25 to 55 ml/min per 100 g, respectively. Regional function decreased sharply when the decrease in these critical ranges of pressure and flow was exceeded.[8] However, Daniell[15] found a direct relation between contractile force and decreased coronary flow except at the extremes of coronary flow levels. Our study, in which progressive decreases in coronary pressure and flow were produced with graded occlusions of the native coronary artery, revealed a significant change in contraction variables of the ischemic zone with 50 percent coronary obstruction. A critical level of obstruction was achieved at a 75 percent reduction of flow, when the contraction variables deteriorated sharply and were indistinguishable from those produced by total coronary occlusion. These contrasting means of decreasing coronary pressure and flow might have been expected to result in different pathophysiologic responses. It is therefore of interest that our findings are not substantially different from those of Wyatt et al. and Daniell.[8,15]

Comparison with S-T and T wave changes: The effects of graded reduction in coronary blood flow on myocardial contractile function closely resemble those on RS-T segment and T wave changes in the local electrogram. Wegria et al.[16] found that a 10 to 35 percent reduction in flow did not produce any electrocardiographic changes. With a reduction of 35 to 70 percent in coronary flow, generally "slight" electrographic changes in both the RS-T segment (S-T elevation) and T wave appeared. With a 70 to 100 percent reduction in flow, there were marked S-T elevations similar to those observed with total coronary occlusion. Maximal electrographic changes were observed in 3 to 5 minutes of sustained reduction in coronary flow. These observations correspond closely to our finding that 75 percent coronary obstruction produced maximal contraction abnormalities similar to those produced by total coronary occlusion.

Comparison with findings after total coronary occlusion: The contractile characteristics of the ischemic zone resulting from a 50 percent reduction in coronary flow closely resembled findings in the border zone after total coronary occlusion previously reported from our laboratory.[2,3,17,18] In both circumstances, there was persistence of the upstroke of the tension curve during the ejection phase despite a decrease in total tension (Fig. 3) and only a mild increase in segment length. This indicates the persistence of contractile function albeit at a reduced level during both the isovolumic and the ejection phases of systole. Similarities are also apparent between the ischemic zone resulting from a 75 percent reduction of coronary flow and the central ischemic zone described after total coronary occlusion (Fig. 3). Both demonstrated loss of ejection tension or a negative slope associated with a marked increase in segment length indicating loss of contractile function throughout systole with paradoxical systolic expansion during the phase of ejection.[2]

Autoregulation of coronary pressure and flow: The finding of a curvilinear relation between pressure and flow distal to the coronary obstruction is interesting. It is well known that changes in perfusion pressure result in similar direct transient changes in coronary blood flow, which later returns toward the previous control level. This phenomenon, termed autoregulation,[19,20] results in a situation whereby relatively severe stenoses are required to alter basal coronary flow significantly. Our observations suggest that when stenosis is severe enough to reduce distal coronary pressure and flow significantly, autoregulatory reserve is probably exhausted (that is, fully utilized) and the major resistance is the stenosis itself and not the distal arteriolar bed.

Potential limitations of study: The limitations in the methodology of our study should be considered. Because the contraction abnormalities were observed during the acute phase only, our findings cannot be extrapolated to the ultimate state of the myocardium resulting from these reductions in coronary blood flow. Although the contractile characteristics of the ischemic myocardium measured by strain gauge and mercury-in-Silastic length gauge can be affected by several factors, including the depth of the sutures and orientation of the gauges, these influences should not significantly affect the serial changes observed in a given experiment.[2–4,17,18,21–24] The severity of partial occlusion in our study was assessed by measuring distal coronary pressure and flow and was not determined by the anatomic extent of the stenosis. Because the coronary flow measured by an electromagnetic flow probe was normalized for 100 g of myocardium, the flow data required measurement of left ventricular mass perfused. In view of the changes in distal perfusion pressures, this could be a source of some error in precise quantitation. It can also be argued that under clinical conditions, the obstructive process is chronically progressive and the experimental study acute. However, one cannot be certain that this is inevitably the case clinically. For example, an acute hemorrhage into a plaque or prolonged coro-

nary spasm could well "acutely" alter pressure-flow relations before compensatory mechanisms occurred.

Clinical implications: If, indeed, the border zone resulting from complete coronary occlusion pathophysiologically resembles the state of the myocardium after a 50 percent reduction in coronary flow and a similar relation exists between the ischemic zone of a complete and a 75 percent occlusion, these data may have relevance to the expected benefits of pharmacologic or surgical interventions. Previous studies on the effects of inotropic and vasodilator agents on the central ischemic, border and nonischemic zones after complete acute coronary occlusion have shown that, although the resultant central ischemic zone is not affected by these interventions, contraction of the border zone improves considerably.[17,18,25–28] It is therefore possible that the amount of myocardium that can be favorably affected decreases significantly when the decrease in coronary blood flow increases from 50 to 75 percent of control values.

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Systolic Honks in Young Children

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Three children with loud systolic honks were studied noninvasively with phonocardiography and echocardiography. It was shown that the precordial honk, like the late systolic mitral murmur and the clicking apical systolic sound, is part of a continuum of auscultatory sounds that result from a defect of mitral valve support and are classified under the general heading of mitral valve prolapse syndrome.

Prolapse of one or both of the mitral valve leaflets is believed to cause the characteristic auscultatory findings of click, murmur or honk. The timing of these sounds in systole varies with different physiologic or pharmacologic maneuvers. Variations in the onset of prolapse are associated with changes in left ventricular end-diastolic dimensions.

The precordial honk or whoop is a unique loud sonorous sound easily recognized on auscultation and by its distinctive pattern in the phonocardiogram. The honk usually arises from hemodynamic events associated with the mitral apparatus, and late systolic murmurs, systolic clicks and systolic whoops constitute a continuum of hemodynamic and accoustical events associated with mitral valve leaflet prolapse and mitral regurgitation.[1–5] We recently studied three girls who were distressed by the sound of a systolic honk, as were their relatives and even physicians not familiar with this problem. The hemodynamic mechanisms responsible for the honk were identified with phonocardiography and echocardiography.

Material and Methods

Echocardiography was performed using a Unirad 100 series ultrasonoscope and 2.25 or 3.5 megahertz transducer of 0.5 inch (1.27 cm) diameter focused at 7.5 cm. The echocardiograms were recorded on strip chart records using the Tektronix recorder. They were obtained with the patients in a 30° left lateral position with the transducer placed in the third or fourth intercostal space oriented perpendicular to the chest wall to allow recording of the mitral valve.

Phonocardiograms were recorded at a paper speed of 100 mm/sec with time markers of 0.02 sec and a low level cut-off filter at 50 hertz on a Hewlett-Packard photographic recorder.

Case Reports

Case 1

A 10 year old white schoolgirl had always had good health and normal exercise tolerance. At age 5 years her parents and other persons standing near by noted an intermittent squeaking sound "like someone rubbing a blown-up balloon" coming from her chest. The noise, which was audible without a stethoscope, was usually heard at the end of the day, when she was tired or, occasionally, after exercise.

She was a normally developed 10 year old girl with no stigmata of Marfan's syndrome. The first heart sound was normal and the second sound split physiologically. There was no third or fourth heart sound or diastolic murmur. A constant mid systolic click heard best at the apex was followed by a blowing or honking mid to late systolic murmur of variable intensity. As the patient moved

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from the supine to the standing position, both the click and the honk occurred earlier in systole and the honk became louder and constant (Fig. 1). Squatting decreased or abolished the honk, and the click moved later in systole. The Valsalva maneuver increased the length of the murmur and caused the click to occur earlier in systole (Fig. 2); phase 4 of the Valsalva maneuver induced honking. Inhalation of amyl nitrite caused the click to occur earlier in systole, and the murmur became softer and longer (Table I). Administration of neosynephrine and hand grip exercise, on the other hand, caused the click to occur later and the honk to appear (Fig. 2).

The echocardiogram revealed late systolic prolapse of both the anterior and posterior mitral valve leaflets (Fig. 3). In addition, there were multiple echoes moving posteriorly in

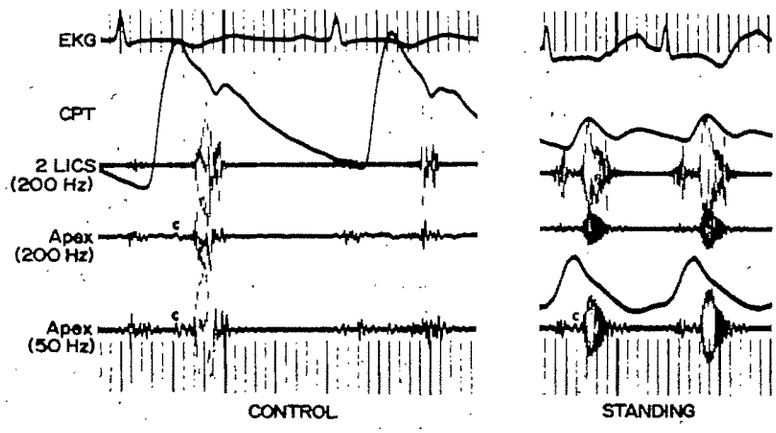


FIGURE 1. Case 1. Phonocardiograms. At supine rest (control) there is a mid systolic click (c) and an intermittent late systolic honk. During standing, the click and honk occur earlier in systole and the honk increases in intensity. ACG = apex cardiogram; CPT = carotid pulse tracing; EKG = electrocardiogram; LICS = left intercostal space.

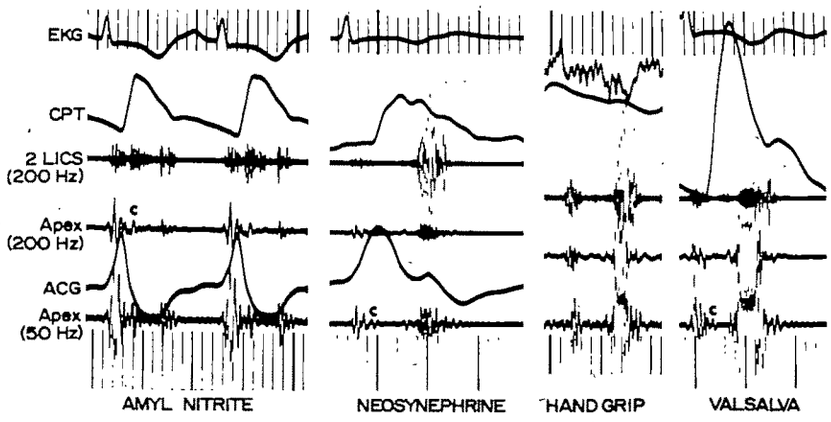


FIGURE 2. Case 1. Phonocardiograms during various pharmacologic and physiologic maneuvers. During amyl nitrite inhalation the systolic "murmur" is virtually holosystolic but decreases in intensity, whereas with neosynephrine and handgrip exercise the murmur increases in intensity, and the click (c) occurs late in systole. The Valsalva maneuver increases the intensity of the honk and causes the click to occur earlier. Abbreviations as in Figure 1.

TABLE I

Physiologic and Pharmacologic Maneuvers in Three Patients with Systolic Honking Murmur

Maneuver	Case 1	Case 2	Case 3
Control	Click constant and murmur grade 1 to 6, blowing to honking	Click variable and murmur grade 1 to 6, blowing to honking	No click and murmur grade 1 to 4, blowing to honking
Amyl nitrite	Click earlier and murmur softer and longer	Click earlier and murmur softer and longer	Murmur longer and softer
Neosynephrine	Click later and honking constant	Not done	Not done
Handgrip	Click later and honking constant	Late systolic honk induced	Late systolic honk induced
Valsalva	Click late and late systolic honking	Murmur louder and honking occasional	Honk induced
Standing	Click earlier and murmur longer; honking induced	Click earlier and murmur longer; honking induced	Honk longer and louder
Squatting	Click and murmur almost disappear	Click unchanged; murmur not present	Honk shorter and softer

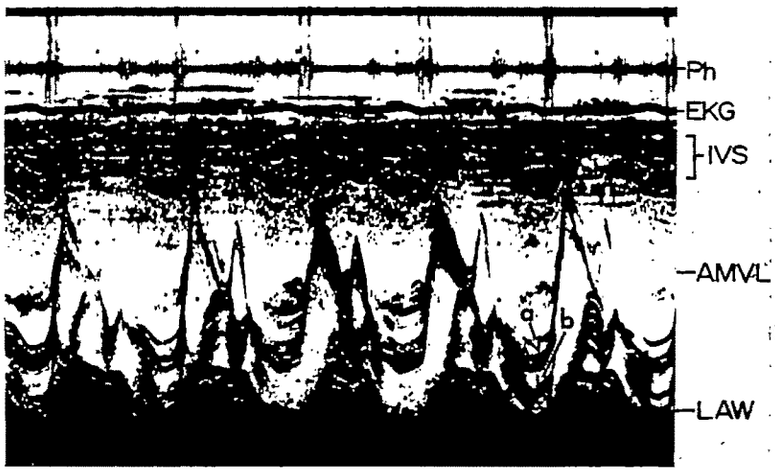


FIGURE 3. Case 1. Echocardiogram and phonocardiogram. The phonocardiogram (Ph) from the apex shows a mid systolic click introducing a late systolic murmur. The echocardiogram shows the anterior (**arrow a**) and the posterior (**arrow b**) leaflets of the mitral valve moving posteriorly in mid systole. Multiple systolic echoes are visible. The murmur corresponds to the period of systolic posterior motion of the mitral leaflets. AMVL = anterior mitral valve leaflet; EKG = electrocardiogram; IVS = interventricular septum; LAW = left atrial wall.

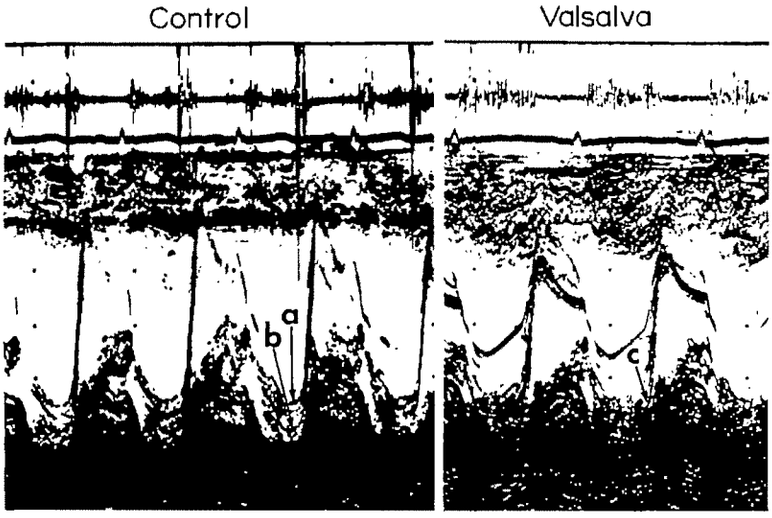


FIGURE 4. Case 1. Phonocardiogram and echocardiogram at rest and during the Valsalva maneuver. The control phonocardiogram shows a mid to late systolic murmur; the echocardiogram shows mid systolic prolapse of both the anterior (**arrow a**) and posterior (**arrow b**) mitral valve leaflets. During the Valsalva maneuver the murmur, which had been mid systolic, becomes virtually holosystolic and the posterior mitral valve leaflet (**arrow c**) shows a pansystolic posterior motion.

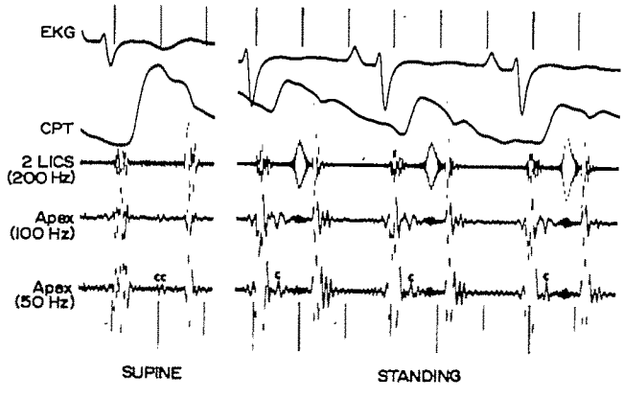


FIGURE 5. Case 2. Supine and standing phonocardiograms. Mid systolic clicks (c) but no definite murmur are present in the control tracing. During standing, a late systolic honk is produced that progressively increases in intensity; the click appears earlier in systole. Abbreviations as in Figure 1.

systole which probably corresponded to redundant chordae tendineae. The Valsalva maneuver produced holosystolic prolapse evident in the echocardiogram (Fig. 4); amyl nitrite inhalation produced a similar echocardiographic response. The electrocardiogram showed a QRS axis of 45°, evidence of left atrial abnormality with notching of the P wave and an abnormal T vector of −60°. The chest roentgenogram was normal.

Case 2

A 13 year old white schoolgirl had always had good health and normal exercise tolerance. At age 8 she first noticed an audible honk that usually occurred when she was upset or excited. The noise, when it occurred, was audible to all persons present in a quiet room, such as a classroom or dining room, and was the cause of considerable embarrassment to the patient. The honk also occurred during physical exercise but was less prominent at that time.

She was a normally developed 13 year old girl with no stigmata of Marfan's syndrome. The first heart sound was normal



FIGURE 6. Case 2. Phonocardiogram (PCG) in various patient positions. In the supine position only mid systolic clicks (c) are present. Sitting produces a soft late systolic honk with slightly earlier systolic clicks. Standing produces a loud mid to late honk with the clicks moving toward the first sound. Squatting eliminates the honk and causes the clicks to occur closer to the second sound. Abbreviations as in Figure 1.

and the second sound split physiologically. There was no audible third or fourth heart sound or diastolic murmur. A soft intermittent systolic click heard best at the apex was followed by a blowing and occasionally honking mid to late systolic murmur of variable intensity. Standing produced an earlier click, a longer murmur and induced the "honk" (Table I), whereas squatting caused the murmur to disappear (Fig. 5 and 6). Amyl nitrite inhalation caused the click to occur earlier in systole and the murmur to become softer but not holosystolic (Fig. 7).

Echocardiography demonstrated mid systolic prolapse of both mitral leaflets. Amyl nitrite inhalation caused the prolapse to become holosystolic (Fig. 8).

Case 3

A 6 year old white schoolgirl had always had good health and normal exercise tolerance and was unaware of any abnormal heart sounds. On routine physical examination her doctor heard a honk and referred her for further diagnostic studies.

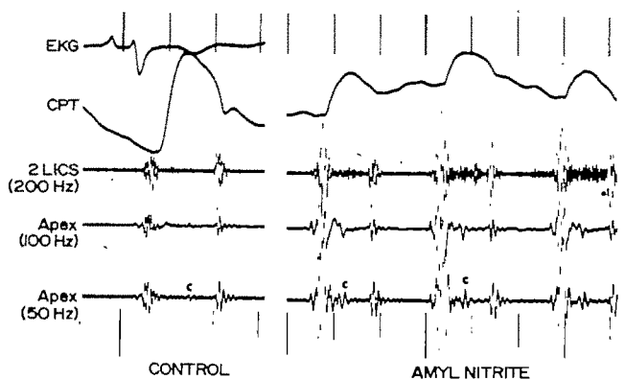


FIGURE 7. Case 2. Phonocardiogram during rest and after amyl nitrite inhalation. There are mid systolic clicks (c), but virtually no systolic murmur at rest (**control**). After amyl nitrite, the murmur becomes holosystolic and progressively increases in intensity and the clicks move toward the first heart sound.

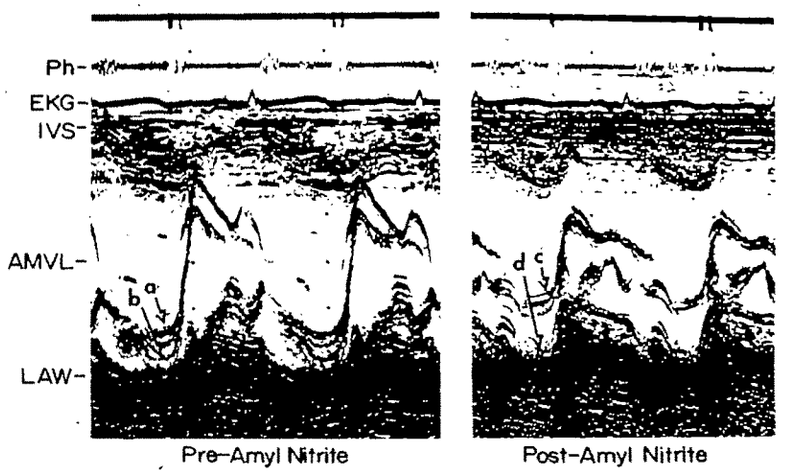


FIGURE 8. Case 2. Echocardiogram and phonocardiogram before and after amyl nitrite inhalation. Before amyl nitrite, there is mid systolic prolapse of both the anterior (**arrow a**) and posterior (**arrow b**) leaflets of the mitral valve. During and after amyl nitrite inhalation, both the anterior (**arrow c**) and posterior (**arrow d**) mitral valve leaflets demonstrate holosystolic prolapse. The phonocardiogram before amyl nitrite shows a mid to late systolic murmur and after amyl nitrite it shows a holosystolic murmur. Abbreviations as in Figure 3.

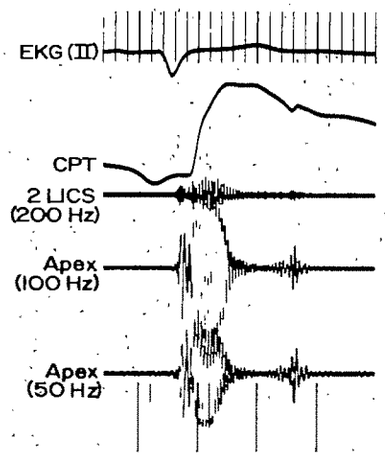


FIGURE 9. Case 3. Phonocardiogram and carotid pulse tracing (CPT) showing a loud, early to mid systolic honking murmur.

She was a normally developed 6 year old girl with no stigmata of Marfan's syndrome. The first and second heart sounds were normal. There was no third or fourth heart sound, diastolic murmur or click. At the apex there was an early systolic murmur that was blowing to honking in character and grade 2 to 4 in loudness (Fig. 9); it was louder on standing and during the Valsalva maneuver (Table I).

Echocardiography revealed holosystolic hammocking of both the anterior and posterior leaflets of the mitral valve. The electrocardiogram showed a QRS vector of +90° and an abnormal T vector of −30°. The chest roentgenogram was normal.

Discussion

The precordial honk or whoop is a medium frequency relatively pure musical tone that is usually crescendo-decrescendo (spindle- or diamond-shaped). As it comes and goes, it may occur with or without a click. McKusick[4] first named these sounds "whoops" because they were reminiscent of the whoop of pertussis. Later, Rackley et al.[1] likened them to the call of wild geese passing through North Carolina and suggested the word "honk." The precordial honk has been found to be associated with billowing of both mitral leaflets even in the absence of mitral regurgitation.[6] The most likely explanation for the honk is that an asymmetric jet escapes from the edge of one prolapsed leaflet and strikes tangentially the bulging surface of the other leaflet.[7] The random behavior of the honk may be due to leaflet resonation rather than actual regurgitation. A precordial honk due to tricuspid regurgitation has also been reported.[8]

Relation to mitral valve prolapse: The precordial honk, like the late systolic mitral murmur and the clicking apical systolic sound, is part of a continuum of auscultatory sounds that result from a defect of mitral valve support and are classified under the general heading of mitral valve prolapse syndrome. This syndrome appears to be a common finding in the general population[9]; the most common subset within this group is the systolic click-murmur or Barlow's syndrome.[10–12] In a few instances mitral valve prolapse has been shown to be associated with myxomatous degeneration of the mitral valve leaflets and chordae tendineae.[13–15] However, there are many other causes of the mitral valve prolapse and systolic mitral clicks are not always accompanied by mitral valve prolapse.[16,17]

Effect of physiologic and pharmacologic maneuvers: Prolapse of one or both mitral valve leaflets is believed to cause the characteristic auscultatory findings of click, murmur or honk. The timing of these sounds in systole varies with different physiologic or pharmacologic maneuvers. Variations in the onset of prolapse are associated with changes in left ventricular end-diastolic dimensions and in the velocity of circumferential shortening during the preprolapse period.[18] With standing or the Valsalva maneuver or amyl nitrite inhalation, the click and murmur or honk occur earlier in systole because a decrease in left ventricular end-diastolic volume causes the prolapse to occur earlier. In the usual patient with mitral valve prolapse the loudness of the murmur may lessen, increase or stay the same. Maneuvers that increase left ventricular end-diastolic pressure, such as squatting, handgrip exercise or phenylephrine administration, cause the click and murmur or honk to occur later in systole.

In addition, maneuvers that tend to change the left ventricular end-diastolic volume and increase the force of myocardial contraction (such as standing) or increase afterload (phenylephrine administration, Valsalva maneuver, handgrip exercise) tend to increase the intensity of the murmur or to induce honking. Afterload reduction with amyl nitrite often decreases the loudness of the murmur or abolishes the honk, although this response is variable.

Occasionally, neither a click nor a murmur is heard at rest and provocative maneuvers are necessary to reveal the typical auscultatory or echocardiographic findings. This is especially true if the patient is not examined in the standing position because auscultatory findings are frequently normal when the patient is supine.

Echocardiographic findings: A characteristic pattern of systolic mitral valve prolapse has been demonstrated echocardiographically.[19–23] Recently, the importance of correct transducer position in the third or fourth intercostal space perpendicular to the chest wall rather than inferior angulation of the transducer has been stressed to eliminate false positive diagnoses.[9,24] Normally the mitral valve echo inscribes a slow continuous anterior motion throughout systole. In mitral valve prolapse, there are two major characteristic patterns of posterior systolic motion of the mitral valve leaflets.[9,21,22] In the first, there is an abrupt mid to late systolic posterior buckling of one or both mitral valve leaflets, more frequently the posterior. In the second, there is a smooth prominent holosystolic bowing (hammocking) of the posterior mitral valve leaflet with maximal posterior excursion at mid systole. The echocardiogram may demonstrate multiple systolic echoes from the mitral valve suggesting separation of the leaflets even when there is no auscultatory or angio-

graphic evidence of mitral regurgitation. This phenomenon is believed to be secondary to the broad echo beam recording interchordal hooding or small aneurysmal leaflet bulges and redundancy at different depths.[22] Although this phenomenon can occur with a normal mitral valve, it is not reproducible from different transducer positions. The echocardiogram is therefore a relatively precise noninvasive means for detecting mitral valve prolapse even in the absence of auscultatory findings. On the other hand, in one series, about 15 percent of patients with angiographically documented mitral valve prolapse had apparently normal echocardiograms.[25] This finding might have been due to technically poor visualization of the posterior mitral valve leaflet or to a limitation in the sensitivity of the procedure because the amount of valve tissue involved in the myxomatous (or other) process might limit its detection.

Clinical significance of systolic honk: Symptoms in mitral valve prolapse are usually absent but some patients have chest pain or palpitations, or both. Occasionally, as with our patients, some patients hear their own honks and are embarrassed, frightened or alarmed by an uninformed physician. Because the mitral valve prolapse syndrome is so benign if bacterial endocarditis can be avoided,[26] its accurate recognition is extremely important. Heart failure, chordal rupture and sudden death are extremely rare, especially in the light of recent evidence suggesting a large prevalence of this disorder.[9] Diagnosis can easily be made on the basis of echocardiography and careful auscultation with the patient standing.

Our patients were reassured that their disorder was benign, no medication was prescribed, and they were instructed in prophylaxis of bacterial endocarditis. If the honk continues to present a social problem, we will consider the use of propranolol to decrease left ventricular contractility and to increase the left ventricular end-diastolic diameter,[26] because both of these maneuvers should decrease the loudness of the honk.

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Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease

III. Methods and Baseline Characteristics, Including Experience With Medical Treatment

By the Veterans Administration Cooperative Group for the Study of Surgery for Coronary Arterial Occlusive Disease*

Report prepared by Katherine Detre, MD, DPH, Herbert Hultgren, MD, FACC and Timothy Takaro, MD

A report of a prospective randomized trial conducted by 13 cooperating hospitals under the auspices of the Veterans Administration to compare the effectiveness of medical and surgical therapy in the management of chronic stable angina pectoris is presented. During a 5-year period, 1,015 men were entered in the study and are now in the follow-up phase. Half were randomly allocated to medical therapy alone (medical group) and half to operative plus medical treatment (surgical group). This report describes the methodology and baseline characteristics of the study group, including, as an additional characterization, survival data in the medical (control) group.

All patients had angina pectoris of 6 months' duration or longer, with electrocardiographic evidence of myocardial ischemia and significant angiographic lesions suitable for aortocoronary bypass grafting. Approximately half had had at least one myocardial infarction (but not within 6 months of entry). Half the patients had significant disease involving three major coronary vessels and 11 percent had left main coronary artery disease; more than half had some abnormality of left ventricular contractility. All but one of 34 baseline characteristics were equally distributed between the medical and surgical groups.

Survival rates of the medical group, based on 2 1/2 years of follow-up, showed wide variations depending on the extent of cardiac disease. The highest survival rates were for patients who had one or two vessel disease with normal ventricular function (survival rate over 90 percent). The lowest rate was for patients with left main coronary disease with abnormal ventricular function (survival rate 65 percent). The baseline characteristics of this patient population were similar in many respects to the reported characteristics of patients in five other study groups with which they are compared.

Coronary arterial surgery, largely for chronic stable angina pectoris, is by far the most common cardiac operation performed in this country today. Many thousands of patients have already been operated upon, and there is general agreement that symptomatic improvement is achieved in many patients. However, there is little agreement about the late effects of the operation. There is no convincing evidence about the prevention of subsequent myocardial infarction and, except for symptomatic patients with left main coronary arterial obstruction,[1] there is continuing uncertainty about whether survival time is increased by surgery.

It has been difficult to determine if survival time in other subgroups is increased by surgery. Most reports have compared survival in surgically treated patients with results obtained from patients with angina who have received medical treatment alone. Generally, three types of medical control groups have been used: (1) patients whose diagnosis was made only by conventional clinical criteria[2–4]; (2) patients who had

* See Appendix for list of participating institutions and persons.

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coronary arteriography[5–10]; and (3) patients who had coronary arteriography and were considered acceptable for coronary arterial surgery. It is clear that the third method, used by McNeer et al.[11] at the Duke Medical Center, provides more accurate data upon which to compare the results of surgical treatment. The Duke control group was not obtained by randomization, but consisted of patients who, for one reason or another, did not have surgery.

The most effective method of evaluating surgical versus medical treatment would be use of a prospective randomized approach to ensure that both treatment groups were as nearly identical as possible. Coronary arteriography should be performed in all patients to determine operability and to define subgroups. In addition, a sufficiently large number of patients should be studied to ensure that statistically significant differences could be evaluated in objectively identified subgroups. In a chronic disease such as stable angina pectoris, a follow-up time of at least 5 years would be desirable. No study reported to date has met all these criteria although some have been met in three randomized investigations reporting on small numbers of patients.[12–14]

After a study of the Vineberg implant operation alone,[15] the Veterans Administration (VA) initiated a large-scale cooperative evaluation of the surgical treatment of stable angina pectoris in 1970, using the methods outlined. At first, both the Vineberg implant and aortocoronary saphenous vein bypass graft operations were studied. However, because the vast majority of patients were randomized in the saphenous vein bypass graft protocol, after 1973 the implant operation was officially discontinued (Table I). This report deals only with patients entered in the study of aortocoronary saphenous vein bypass surgery.

This paper describes the methodology of this study and the baseline characteristics of the study group and presents preliminary data on survival in the medical (control) group as an additional method of characterizing the study group as a whole.

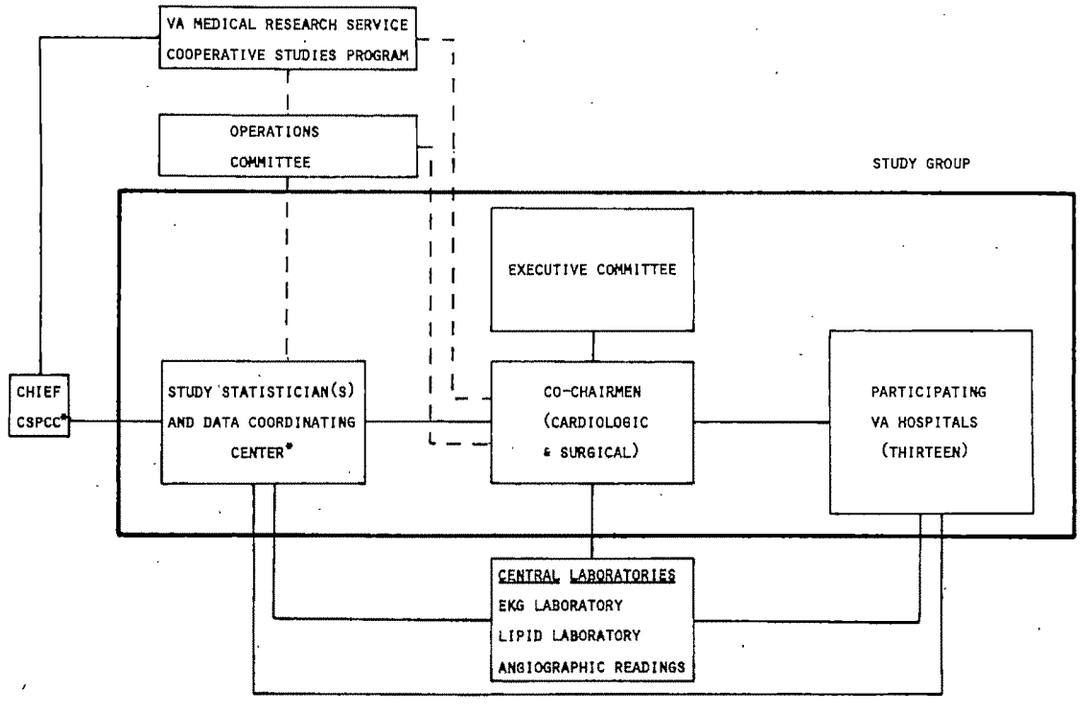
TABLE I

Chronologic Development of the Study*

	Implant	SVBG
1968 to 1969 Randomized Cooperative Study, Vineberg implant:	75	7†
1970 to 1971 Randomized Study, implants and SVBG:	28	322
1972 to 1974 Cooperative Study restarted:	2	686
Totals	105	1015

*Only patients randomized in the saphenous vein bypass graft (SVBG) protocol are considered in this report.
†2 hospitals began randomization in the saphenous vein bypass graft protocol in the final months of 1969.

DIAGRAM OF RELATIONSHIPS OF KEY BODIES IN THE VA COOP STUDY OF CORONARY ARTERIAL SURGERY



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FIGURE 1. Organizational structure of the Veterans Administration Cooperative Study of surgery for coronary arterial occlusive disease.

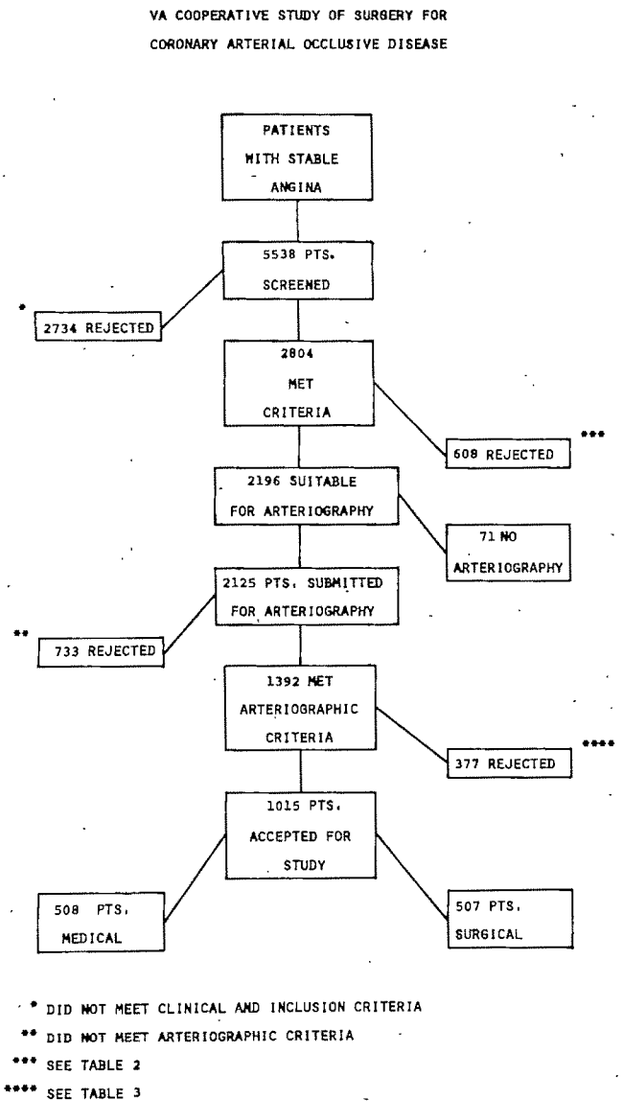


FIGURE 2. Disposition of patients from screening to randomization in the cooperative study. PTS. = patients.

Design and Methods

Of 21 Veterans Administration hospitals that met established requirements and were invited to join the collaborative study, 13 remained active, recruiting together a total of over 1,000 patients. Because the eight other hospitals together entered fewer than 30 patients, these hospitals and their entries were excluded from the study and are not considered in the final analysis.

Screening and selection of patients—criteria for entry: All men who were admitted to the participating Veterans Administration hospitals with the diagnosis of angina pectoris were considered for the study. The names of all such patients were entered on a screening log, and each patient was then submitted to a screening process to determine his suitability for inclusion in the study. Criteria for entry into the study consisted of: (1) stable angina pectoris of more than 6 months' duration, with acceptable medical management (which could include the use of nitroglycerin, propranolol, isosorbide dinitrate and other measures), of at least 3 months' duration; (2) no contraindications to saphenous vein bypass graft surgery; (3) electrocardiographic evidence of healed myocardial infarction or abnormal T waves or S-T segments in the resting electrocardiogram compatible with myocardial ischemia. In the absence of these findings, an electrocardiographically positive exercise test was required.

Each patient was also evaluated for specific disqualifying conditions: (1) myocardial infarction less than 6 months before operation; (2) persistent diastolic hypertension (more than 100 mm Hg) despite treatment; (3) marked cardiac enlargement, presence of ventricular aneurysm or other significant cardiac disease such as valvular heart disease; (4) presence of any other major disease making major surgery inadvisable or limiting life expectancy to less than 5 years; (5) participation by the patient in any other Veterans Administration Cooperative Study; (6) previous operation for angina pectoris; (7) unstable angina or angina of increasing severity, suggesting "impending infarction"; and (8) presence of congestive heart failure unless clinically compensated for at least 3 weeks. (Age and controlled diabetes were not contraindications.)

Informed consent: Patients who met the criteria for the study up to this point were interviewed by a physician, and the nature and need for the study were explained. The advantages, disadvantages and risks of both methods of treatment were described. The patient was made to understand that it was not known which treatment was the better therapy. If he agreed to enter the study, he was required to sign a Veterans Administration form authorizing use of procedures for investigational purposes.

Arteriography: The names of patients who met the eligibility requirements and who formally consented to participate in the study were recorded in arteriography logs, and coronary arteriography and left ventriculography were performed. The films were evaluated by an angiographic team, consisting usually of a cardiologist, the angiographer and a cardiac surgeon, to determine whether the patient was angiographically suitable for the study. The angiographic criteria stated that the angiogram must reveal, in at least one plane, reduction of the luminal diameter by 50 percent* or greater in one or more of the major vessels supplying either the anterolateral or posteroinferior wall of the left ventricle, or both. In addition, the vessel distal to the occluded area must be suitable for grafting, there must be no evidence of ventricular aneurysm and sufficient myocardial contractility must be preserved to permit surgery with a reasonable surgical risk. Myocardial contractility was judged by observation and categorization of four ventricular segments of the left ventriculogram and by calculation of the ejection fraction.[16]

Randomization process: Patients who were eligible arteriographically were randomly allocated to medical or surgical therapy within several groups stratified according to age (under 50 years or 50 years and older) and angiographic findings. Patients with arteriographic lesions involving only the anterolateral myocardial wall or only the posteroinferior wall were categorized together but separately from those with involvement of both regions. The randomization process was initiated at each hospital and completed at the Data Coordinating Center by telephone. If surgery was assigned, the patient was scheduled for operation as soon as possible. (In 55 percent of the cases this took place within 1 month.) Myocardial scar resection, valve surgery or aneurysmectomy were not performed. Patients in both groups (medical and surgical) received maximal medical therapy to suppress symptoms, including short- and long-acting vasodilators and propranolol. Data regarding medications given were collected in all patients but no uniform medical regimen was used.

* This was considered to be the equivalent, in most instances, of a 75 percent reduction in the area of the cross section of the lumen at this point.

Follow-up protocol: All patients were to be seen at 3 month intervals. One year after entry, all patients were to be hospitalized for a complete clinical evaluation. Coronary arteriography was not required at 1 year, but saphenous vein bypass graft angiography was to be performed in all surgical patients who agreed to this procedure.

At quarterly, semiannual and annual follow-up visits, examination and electrocardiography were performed. In addition, semiannually, an angina questionnaire was completed, and annually, pertinent laboratory data were collected.

Delinquent follow-up: In addition to assiduous efforts by the participating hospitals to maintain the prescribed follow-up record for each patient, periodic monitoring of the records was done at the Data Coordinating Center by computer to identify those patients whose follow-up was notably delinquent (patients who missed two or more scheduled visits). The names of these patients were then submitted to a Veterans Administration central data file called the Beneficiary Identification and Records Locator Subsystem (BIRLS) for retrieval of survival information. Because of the nature of the BIRLS record system, a 98 percent follow-up with regard to survival data at any one time was ensured. This was confirmed by an actual test of the BIRLS system, using known deaths in the study. The Veterans Administration Patient Treatment Files were also used to obtain information concerning the patient's most recent hospitalization in any other Veterans Administration facility.

Organizational structure: The relations of the key bodies in the study are depicted in Figure 1. The sponsoring organization (The Cooperative Studies Program of the Medical

TABLE II

Disposition of Patients Screened

Patients Not Eligible for Study (N_1 = 2734)			Patients Eligible for Study (N_2 = 2804)		
	Patients (no.)	Percent of N_1		Patients (no.)	Percent of N_2
Reason for rejection			Entered in arteriographic logs	2196	78
Previous cardiac surgery	119	4	Rejected for study	608	22
Death	51	2			
Participant in another VA cooperative study	31	1	Reason for rejection		
Presence of other serious disease	443	16	Unwilling to enter study	208	7
Did not meet ECG criteria	528	19	Unreliable or unable to cooperate in study	129	5
Insufficient angina	724	26	Age	44	2
Myocardial infarction within last 6 months	403	15	Other	227	8
Presence of myocardial decompensation	183	7	Total	608	100
Presence of cardiomegaly	61	2			
Presence of ventricular aneurysm	65	2			
Presence of persistent hypertension despite treatment	44	2			
Referred for surgery	82	3			
Total	2734	100			

ECG = electrocardiographic; pts = patients.

TABLE III

Disposition of Patients After Arteriography

Patients Not Eligible for Study (N_1 = 733)			Patients Eligible for Study (N_2 = 1392)		
	Patients (no.)	Percent of N_1		Patients (no.)	Percent of N_2
Reason for rejection			Randomized	1015	73
Presence of ventricular aneurysm	160	22	Rejected	377	27
Poor myocardial contractility	134	18	Reason for rejection		
Nonsignificant angiographic lesions	297	41	Unwilling to enter study	142	10
Insufficient symptoms	81	11	Unreliable or unable to cooperate in Study	25	2
Referred for surgery	4	.5	Death	29	2
Temporarily rejected	7	1	Other	181	13
Participant in another VA Cooperative Study or previous cardiac surgery	7	1	Total	377	100
Complications at arteriography	5	.6			
Arteriography technically unsatisfactory	24	3			
Marked elevation of LVEDP	14	2			
Total	733	100			

LVEDP = left ventricular end-diastolic pressure.

Research Service of the Veterans Administration), the Operations Committee (made up of recognized senior cardiologists and surgeons outside the Veterans Administration system, to advise and monitor the study) and the director of the Cooperative Studies Program Coordinating Center all played important supportive roles. The study group proper consisted of the 13 participating hospitals, the Executive Committee, the cardiologic and surgical cochairmen, the study statisticians and the Data Processing Center. In each participating hospital, a cardiologist and a cardiac surgeon were designated official coinvestigators.

In addition, three Central Laboratories were designated. The Veterans Administration Cooperative Studies Lipid Laboratory at Durham, North Carolina, performed the initial lipid typing and serum cholesterol and triglyceride determinations on blood samples collected and shipped from the participating hospitals. The Minnesota Electrocardiographic Laboratory at the University of Minnesota in Minneapolis has been designated to perform a centralized reading of all initial, first quarterly and annual electrocardiographic tracings using the standardized Minnesota coding format.

During the early years of the study, it became evident that a great deal of variability might exist among observers in the interpretation of coronary angiograms.[17] Therefore, all angiograms were reviewed by the investigators, and a central reading laboratory* was designated to code at least 200, and possibly all, of the baseline angiograms. These special studies will be reported upon in detail at a later date.

Results

Patients screened and entered into the study: From January 1970 to December 1974, a total of 5,538 patients with stable angina were screened for eligibility and willingness to enter the study. Of this group, 2,125 had coronary arteriography and 1,015 patients were randomized in the saphenous vein bypass graft protocol (Fig. 2). Patient entry into the study was discontinued on December 31, 1974.

The reasons for rejection at the time of initial screening and after coronary arteriography are summarized in Tables II and III. The total number of patients screened and subjected to arteriography and randomized treatment during the 5 calendar years of patient intake are displayed in Table IV. Of the 5,538 patients screened, approximately half were rejected, primarily for four reasons: insufficient angina, other serious disease, lack of electrocardiographic evidence of coronary artery disease and an acute myocardial infarction occuring within 6 months before consideration for the study. These four reasons accounted for 77 percent of the rejections of screened patients (Fig. 2) (Table II).

Of the 2,196 patients considered acceptable for the study, 2,125 agreed to undergo coronary arteriography. One third of these patients did not meet the arteriographic criteria of the protocol. Of those who did, 73 percent were actually randomized (Fig. 2). The reasons for rejection of the remaining 27 percent are noted in Table III. Thus, the yield from initial screening to entry into the study was about 6 to 1, but the yield of patients eligible on the basis of *both* screening and arteriographic criteria was about 1.4 to 1.

In spite of every reasonable effort to select patients who were both suitable and willing to accept the treatment assigned, approximately 7 percent of the patients in each of the treatment groups did not adhere to the prescribed regimen during patient intake. When patient accession ended on December 31, 1974, there were 40 "medically randomized-operated on" patients and 33 "surgically randomized-not operated on" patients.

Baseline characteristics: The distribution of some baseline descriptors is given in Tables V through IX. The mean age of the study population was 50.5 years (range 27 to 68 years).

The distribution of eight baseline variables related to cardiovascular history was very similar in both treatment groups (Table V). Approximately half the patients had at least one myocardial infarction and an additional 8 percent had more than one. The median duration of angina was approximately 28 months. More than half the patients had severe functional limitation according to the New York Heart Association classification.[18]

The cardiothoracic ratio, blood pressure and serum cholesterol for the two treatment groups are listed in Table VI. Approximately 27 percent of the patients had a diastolic pressure of 90 mm Hg or more. Again, the distribution of variables was similar in both treatment groups. In only one instance was there a statistically significant difference (serum cholesterol).

Electrocardiographic variables were also approximately equally distributed in the two treatment groups (Table VII).

The angiographic baseline findings (Table VIII) indicate that 70 percent of the patients had some left ventricular abnormality. Approximately 27 percent had abnormal left ventricular size, more than 50 percent had some abnormality of left ventricular contractility, 33 percent had left ventricular end-diastolic pressure over 14 mm Hg and 15 percent had a low ejection fraction (less than 0.45). One-half of all patients had three vessel disease as defined by significant lesions of the left anterior descending, the left circumflex (or circumflex marginal branches) and right coronary arteries. Eleven percent had a significant left main coronary arterial lesion.

The distribution of composite risk variables is shown in Table IX. Single vessel disease with normal left

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TABLE IV

Number of Patients Screened, Subjected to Arteriography and Randomized

Year	1970*	1971	1972	1973	1974	Totals
Total number of patients screened	740	1189	1339	1250	1020	5538
Total number subjected to arteriography	264	457	531	490	383	2125
Total number randomized	118*	211	267	252	167	1015

*Seven patients randomized in final months of 1969.

ventricular function was present in only 55 patients (5.4 percent). The largest subgroup (38 percent) consisted of patients with three vessel disease and abnormal left ventricular function. The latter was defined as one or more of the following: abnormal left ventricular size or cardiothoracic ratio greater than 49 percent, some abnormality of contractility, ejection fraction less than 0.45 or left ventricular end-diastolic pressure more than 14 mm Hg.

These data indicate that the study group contained a significant proportion of patients with a relatively severe degree of chronic angina associated with a large

TABLE V

Distribution of Variables Relating to Patients' History*

Variable		Medical		Surgical		Total	
		no.	%	no.	%	no.	%
New York Heart Association classification	I	16	3.1	13	2.6	29	2.9
	II	202	39.8	197	38.9	399	39.3
	III	274	53.9	282	55.6	556	54.8
	IV	14	2.8	14	2.8	28	2.8
History of previous MI	None	200	39.4	193	38.1	393	38.7
	1 MI	262	51.6	279	55.0	541	55.3
	2+ MI	45	8.9	35	6.9	80	7.9
Duration of angina (mo)	0–5	21	4.1	19	3.7	40	3.9
	6–12	136	26.8	116	22.9	252	24.9
	13–24	91	17.9	94	18.5	185	18.2
	25–60	123	24.3	150	29.6	273	26.9
	>60	136	26.8	128	25.2	264	26.0
History of hypertension	No	364	71.7	382	75.3	746	73.5
	Yes	143	28.1	125	24.7	268	26.4
History of CHF	No	465	91.5	479	94.5	944	93.0
	Yes	42	8.3	28	5.5	70	6.9
History of CVA	No	487	95.9	495	97.6	982	96.7
	Yes	20	3.9	12	2.4	32	3.2
History of diabetes	No	430	84.6	434	85.6	864	85.1
	Yes	77	15.2	73	14.4	150	14.8
History of family CVD	No	193	38.0	195	38.5	388	38.2
	Yes	314	61.8	310	61.1	624	61.5

*For certain variables shown in Tables V to IX, the totals are not equal to 100 percent because some of the baseline data are unknown. CHF = congestive heart failure; CVA = cerebral vascular accident; CVD = cardiovascular disease; MI = myocardial infarction.

TABLE VI

Distribution of Miscellaneous Variables (Cardiothoracic Ratio, Blood Pressure, Serum Cholesterol)

Variable		Medical		Surgical		Total	
		no.	%	no.	%	no.	%
Cardiothoracic ratio	0–49	416	81.9	413	81.5	829	81.7
	49+	49	9.6	50	9.9	99	9.8
Systolic blood pressure (mm Hg)	0–99	3	0.6	5	1.0	8	0.8
	100–109	41	8.1	33	6.5	74	7.3
	110–119	89	17.6	69	13.6	158	15.6
	120–129	115	22.7	138	27.2	253	25.0
	130–139	100	19.7	116	22.9	216	21.3
	140–149	83	16.4	84	16.6	167	16.5
	150–159	32	6.3	31	6.1	63	6.2
	160–169	21	4.1	14	2.8	35	3.5
	170–179	10	2.0	11	2.2	21	2.1
	179+	12	2.4	6	1.2	18	1.8
Mean	...	129.3		128.8		...	
Diastolic blood pressure (mm Hg)	0–69	32	6.3	33	6.5	65	6.4
	70–79	117	23.1	117	23.1	234	23.1
	80–89	212	41.8	224	44.8	439	43.3
	90–99	106	20.9	103	20.3	209	20.6
	99+	39	7.7	26	5.1	65	6.4
Mean	...	81.9		81.8		...	
Serum cholesterol (mg/100 dl)	0–212	62	25.5*	98	39.9*	160	32.3
	213–249	89	36.6	90	35.7	179	36.2
	249+	92	37.9*	64	25.4*	156	31.5

*$P = 0.002$.

incidence of prior infarction, ST-T wave abnormalities, multiple vessel disease and poor left ventricular function.

Examination of the distribution of variables between the medical and surgical treatment groups reveals only one significant difference between the groups (serum cholesterol levels). Randomization, therefore, was successful in providing two relatively homogeneous groups for the purposes of this study.

Survival characteristics of the control group: In addition to the characterization of the patients with baseline variables, the natural history experienced by

TABLE VII

Distribution of Electrocardiographic Variables*

ECG Variable		Medical		Surgical		Total	
		no.	%	no.	%	no.	%
Myocardial infarction	None	196	39	184	36	380	37
	Possible	62	12	76	15	138	14
	Probable	40	8	32	6	72	7
	Definite	133	26	136	27	269	27
S-T depression	None	166	33	173	34	339	33
	Minor	248	49	244	48	492	49
	Major	17	3	11	2	28	3
S-T elevation	None	419	83	417	81	836	82
	Minor	7	1	9	2	16	2
	Major	5	1	2	1	7	1
Ventricular aneurysm	No	422	83	413	81	835	83
	Yes	9	2	15	3	24	2
LV hypertrophy	No	409	81	415	82	824	81
	Yes	22	4	13	2	35	4
PVCs	No	417	82	413	81	830	82
	Yes	14	3	15	3	29	3
Ventricular conduction defects	No	419	82	420	83	839	83
	Yes	12	3	8	1	20	2
Left axis deviation	No	424	83	426	83	850	84
	Yes	7	2	2	1	9	1
Abnormality in resting ECG	No†	93	18	92	18	185	18
	Yes	338	67	336	66	674	67

*Approximately 15 percent of the baseline electrocardiographic data has not yet been recorded.
†This implies that patient had a positive exercise electrocardiogram.
ECG = electrocardiographic; LV = left ventricular; PVC = premature ventricular contractions.

TABLE VIII

Distribution of Variables Related to Coronary Angiographic Findings

Variable		Medical		Surgical		Total	
		no.	%	no.	%	no.	%
LV function*	Normal	129	25.4	124	24.5	253	25.0
	Abnormal	357	70.4	356	70.2	713	70.3
LV size	Normal	364	71.7	376	74.2	740	72.9
	Abnormal	142	28.0	128	25.2	270	26.6
LV contractility	Normal	226	44.5	232	45.8	458	45.1
	Abnormal	281	55.3	271	53.5	552	54.4
Ejection fraction	45+	388	80.3	387	78.0	775	79.2
	0–44	72	14.9	75	15.1	147	15.0
LVEDP	0–14	315	62.0	328	64.7	643	63.4
	>14	173	34.1	166	32.7	339	33.4
Collateral vessels	No	165	33.1	138	27.5	303	30.3
	Yes	333	66.9	361	72.1	694	69.5
Number of vessels with significant disease	One	84	16.5	76	15.0	160	15.8
	Two	166	32.7	168	33.1	334	32.9
	Three	257	50.6	263	51.9	520	51.2
Left main lesion	0–49%†	452	89.0	443	87.4	895	88.2
	50–100%†	53	10.4	60	11.8	113	11.1

*Left ventricular (LV) abnormality is defined as abnormal left ventricular size or cardiothoracic ratio (ratio >0.49), abnormal left ventricular contractility, left ventricular end-diastolic pressure >14 mm Hg or ejection fraction <45 percent.
†Percent reduction in diameter of lumen.

TABLE IX

Distribution of Composite Risk Variables*

Number of Diseases Vessels and LV Function	Medical		Surgical		Total	
	no.	%	no.	%	no.	%
1 vessel disease with normal LV function	29	5.7	26	5.1	55	5.4
2 vessel disease with normal LV function	34	6.7	37	7.3	71	7.0
3 vessel disease with normal LV function	56	11.0	58	11.4	114	11.2
1 vessel disease with abnormal LV function†	42	8.3	42	8.3	84	8.3
2 vessel disease with abnormal LV function†	105	20.7	108	21.3	213	21.0
3 vessel disease with abnormal LV function†	192	37.9	194	38.3	386	38.1

*There are 50 medical and 42 surgical patients whose risk category is unknown because one or more factors that define left ventricular function or number of diseased vessels are unknown.

†Abnormal left ventricular (LV) function is defined as for Table VIII.

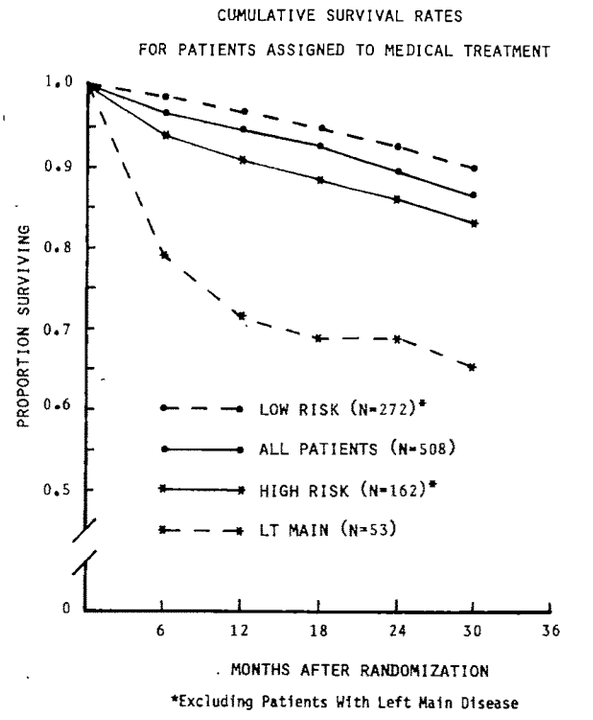


FIGURE 3. Cumulative survival rates of patients assigned to the medical (control) group. The "high risk" group includes patients with three vessel disease and some abnormality of left ventricular function but excludes patients with left (LT) main coronary artery disease. "Low-risk" patients are all others, excluding again, patients with left main coronary artery disease. (Twenty-one patients were assigned to "unknown risk" group because of insufficient data.) N = number of patients.

the group assigned to medical treatment during a 2 1/2 year follow-up further reflects the severity of the cardiovascular status of some of the subgroups of the patient population. Figure 3 shows the survival results (total mortality) by life table analysis in all patients randomized to medical treatment, as well as in those with a significant left main coronary lesion and in patients at "low" and "high" risk. A high risk patient was defined as one with three vessel disease and some abnormality of left ventricular function. A low risk patient was defined by default as one not in the high risk group or one with undertermined risk because of incomplete data (92 patients, 50 medically and 42 surgically randomized).

For the medically treated group as a whole, the mortality rate at 2 1/2 years of follow-up was 13 percent. The high risk group showed a higher mortality rate of 17 percent at 2 1/2 years, and the patients with a significant left main coronary arterial lesion had the highest mortality rate of 35 percent. It seems clear that the presence of left main coronary artery disease and, to a lesser extent, of some abnormality of left ventricular function with three vessel disease adversely affects survival. Figure 4 shows the cumulative survival curves of the six previously defined groups presented in Table IX and of the group of patients with significant left main coronary arterial lesions. It is clear that groups 5 and 6 with two and three vessel disease and some abnormality of left ventricular function, as well as the groups with a left main coronary arterial lesion with and without left ventricular abnormality, have the lowest survival rates.

To examine the validity of the particular definition of abnormality of left ventricular function that we had selected, we created another high risk group. In this group, also characterized by triple vessel disease, instead of requiring additional abnormality in left ventricular size, contractility or elevated end-diastolic pressure or depressed ejection fraction, we required only the identification of abnormality in left ventricular contractility. This group showed a 16 percent 2 1/2 year mortality rate, which is almost identical to that of the larger group, indicating that the other criteria were equally valid characterizers of abnormality of left ventricular function. In particular, there was concern about the inclusion of elevated left ventricular end-diastolic pressure as the sole characterizer because this variable is known to be affected by ventricular compliance; heart rate, fluid-filled catheter systems and other factors. However, a survival analysis of patients with three vessel disease who had elevated end-diastolic pressure as their only criterion of left ventricular abnormality showed a 22 percent 2 1/2 year mortality rate. Considering the small sample size of this group (18 patients), this mortality rate, though even higher than that of the previously described group, is not significantly different from that of our original high risk group.

As the risk of a group increases from low to high, the survival curve over time also changes, indicating a higher initial mortality rate in the higher risk groups. Although there were only a small number of patients in some of these subgroups, the implication of our findings is that when only one, two or three vessels are diseased and left ventricular function remains normal the survival rates tend to cluster at about the 95 percent level

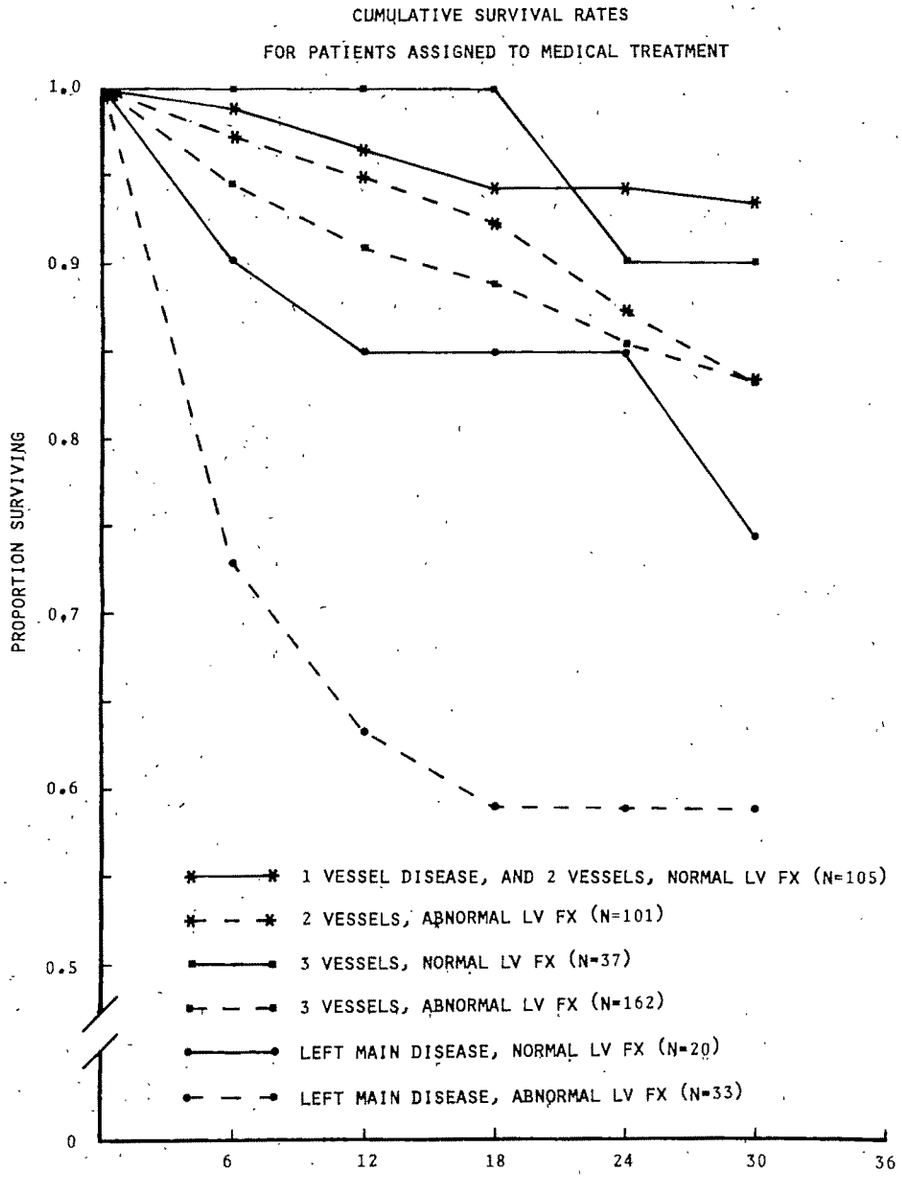


FIGURE 4. Cumulative survival rates for six subgroups of medically treated patients. Patients with left main coronary lesions have been excluded from all groups except the last two, as noted. LV FX = left ventricular function; N = number of patients.

at 18 months. At this follow-up interval, survival rates for patients with three vessel disease and abnormal left ventricular function and for those with left main disease and normal left ventricular function seem to be similar (between 85 and 90 percent). In contrast, patients with left main coronary arterial lesions and an identifiable abnormality of left ventricular function showed only a 60 percent survival rate at 18 months.

Discussion

Randomized trials versus retrospective studies: Although randomized clinical trials of various drug treatment regimens are commonplace, there have been few long-term control studies of operative procedures, and very few indeed of surgery for chronic coronary arterial occlusive disease. Those few thus far reported[12–14] involved relatively few patients (up to 100), yielding even smaller control and treatment groups and making analyses in subgroups impractical. An ongoing study sponsored by the National Institutes of Health may involve more substantial numbers of patients. Characterization of the study group and preliminary results of this study are not yet available.

An alternative approach has been taken by the Duke group of investigators referred to previously.[11] On the basis of the thesis that therapeutic decisions in chronic disease tend to be made randomly with respect to distant goals, the investigators compared retrospectively 379 consecutive surgically treated patients who had stable angina pectoris with 402 patients treated medically. Although their assumption is provocative, its validity deserves to be examined. In 21 of the 89 baseline variables characterizing the study population, there was a significant difference ($P < 0.05$) in distribution be-

tween the two treatment groups, whereas only four significant differences could have been expected on a random basis if their assumption were correct. Several of the 21 variables were interdependent. However, some, such as poor left ventricular function, are known to be important predictors of risk. Because the medically treated group as a whole had poor left ventricular function, it could be expected that when comparing treatment results surgical treatment might appear to be more advantageous, because the patients who received surgery were at lower risk to begin with. Although this problem can be compensated for by statistical methods, it indicates that randomness of the judgment about treatment allocation is doubtful. Presumably, many factors other than the 89 baseline descriptors must contribute to such a medical judgment. Although we agree with McNeer et al.[11] that randomized trials are costly and time-consuming, requiring large numbers of patients, we recognize that these requirements arise from the nature of the disease and therapy, and not from the choice of research method. If, as they suggest, a randomized trial were conducted only for the higher risk patients who tended to show more favorable response to surgery in their study, this approach would reduce cost, time and number of patients. However, an important medical and ethical question would be unanswered: Are there subgroups of patients who in the long run will not benefit or may even be adversely affected by surgery? For these reasons, we remain convinced that, although useful information may well emerge from the retrospective matched approach, the least biased and thus most objective design for studying survival results of coronary bypass surgery and coronary heart disease is the randomized clinical trial.

Use of 50 versus 75 percent coronary stenosis as angiographic criterion: The use of the angiographic criterion for entry into the study, which calls for reduction of the luminal diameter by 50 percent or greater in at least one plane in one or more of the major vessels, may be criticized. This criterion rests upon two bases. One, there is ample precedent for the use of this criterion in many studies.[19–24] Although other studies have used more stringent criteria,[11,14,25–27] at the time the Cooperative Study protocol was written (in 1969) the 50 percent level was judged appropriate. We recognize that in some instances, due to foreshortening, a lesion seen in one oblique plane may not be identified in the opposite oblique view. Conceivably, it might not in fact be present in the other plane. Even under these circumstances, however, a 50 percent lesion can be shown to be hemodynamically significant—when coronary blood flow requirements are increased.[28]

In later analyses, there will be an opportunity to review the outcome in patients in two subgroups, those with lesions of 50 to 75 percent reduction in luminal diameter and those with 76 percent or greater reduction. These data are not yet available.

Use of elevated left ventricular end-diastolic pressure as a sign of poor left ventricular function: This seems to have been warranted in view of the mortality rate in the group of patients with three vessel disease in which this was the sole abnormal index of left ventricular function. For this reason, it seemed appropriate to classify these patients with the high risk rather than with the low risk group. In these patients, elevated left ventricular end-diastolic pressure apparently reflects ischemia at rest rather than an abnormality in contractile function.

TABLE X

Prevalence of Baseline Characteristics in Duke Study[29] and VA Cooperative Study

Characteristic	Duke Study (%)	VA Study (%)
Male sex	87	100
Age less than 50 years	46	44
History of angina	98	100
History of hypertension	34	26
History of diabetes	11	15
History of congestive failure	14	7
ECG variables:		
Left ventricular hypertrophy	2	4
Evidence of old MI	51	56
LBBB, RBBB	4	3
Resting ST-T wave changes	40	63
Cardiomegaly	12	10
Angiographic variables		
One vessel involved	19	16
Two vessels involved	31	33
Three vessels involved	50	51
Left main lesion	12	11
LV contraction abnormality	52	54

ECG = electrocardiographic; LBBB = left bundle branch block; LV = left ventricular; MI = myocardial infarction; RBBB = right bundle branch block.

Is the study population representative?: The patient population in this study is not considered a random sample of men with stable angina pectoris. The patients were selected by (1) their status as veterans, (2) their motivation and willingness to participate in the study, and (3) their ability to satisfy the comprehensive screening, arteriographic and inclusion criteria described. One might therefore question whether the population of the Veterans Administration study group is comparable with patients who are being selected for saphenous vein bypass graft surgery in private or academic medical-surgical centers in the United States. In an attempt to answer this difficult question, we have compared selected significant baseline characteristics of the surgical treatment group from a more recent study from Duke,[29] with similar characteristics of the Veterans Administration study population (Table X). Patients in the Duke study had a greater incidence of congestive failure and hypertension, whereas Veterans Administration patients included more with ST-T wave changes in resting electrocardiograms. In other descriptors, no significant differences were present and the two study groups seem to have been essentially similar.* A similar comparison was made with baseline characteristics in the McNeer report from Duke.[11] Again there were some differences, but no indications

* Data using the New York Heart Association classification were omitted because of substantial differences in definitions used by the two groups of investigators.[30]

TABLE XI

Analysis of Variability Among Participating Hospitals

Hospital	Patients Randomized (no.) Medical	Surgical	Total	Percent "Low Risk" Patients*	Percent "High Risk" Patients†
1	11	14	25	84	16
2	42	43	85	73	27
3	26	24	50	38	62
4	61	59	120	72	28
5	74	74	148	63	37
6	78	75	153	59	41
7	14	18	32	81	19
8	37	37	74	61	39
9	30	30	60	70	30
10	32	32	64	55	45
11	70	66	136	50	50
12	11	12	23	78	22
13	22	23	45	51	49
Total patients randomized			1015	62	38

*"Low risk" patients are defined as all patients not characterized as "high risk."

†High risk patients are defined as patients with three vessel disease plus some abnormality of left ventricular function.

that the Veterans Administration study population was not representative of men in this age group with coronary artery disease.

Differences among participating hospitals: Another problem relates to comparability of participating hospitals with regard to numbers of subjects entered into the study, the relative proportions of good risk and poor risk patients, uniformity of performance and interpretation of angiograms, surgical expertise and other variables. Table XI displays the variability of numbers and the characterization of the patients. The widest variation in characterization of the patients occurred in the hospitals contributing the fewest patients.

We have alluded to the recognition of interobserver and intraobserver variability of arteriograms and our attempt to cope with this problem. The surgical experience will be reported in detail elsewhere. Suffice it to say that there were significant differences in operative (30 day) mortality among hospitals, especially when less experienced teams are compared with those more experienced in the early years of the study. This finding was responsible for the decision to restart the study in 1972, when all hospitals had gained sufficient and approximately equal expertise in both angiography and surgery. As can be seen from Table IV, approximately 70 percent of the patients who were entered into the saphenous vein bypass graft study were randomized after this date.

Programs and survival rates among subgroups: Longitudinal studies based upon clinical features and angiographic data permit analysis of prognosis of identifiable subgroups. Details from five such studies[6–11,30] are tabulated with data from the Veterans Administration Cooperative Study in Table XII. These studies present surprisingly comparable data with regard to the prognosis of single vessel disease, with a 2 year survival rate ranging between 90 and 100 percent and a mean survival rate of 95 percent in 657 patients. In patients with two vessel disease, three studies are in close agreement with the Veterans Administration Cooperative Study data, with an overall survival rate ranging from 90 to 93 percent. However, two studies report lower survival rates of 79 and 74 percent, respectively.

There is still greater diversity in 2 year survival rates in patients with three vessel disease. These studies report a range from 63 to 82 percent (average 71 percent) compared with the Veterans Administration Cooperative Study rate of 88 percent. Thus, in the total of all

TABLE XII

Survival Rates in Veterans Administration Cooperative Study Subgroups Compared With Rates in Published Studies (Two Year Survival)

	VA Study*		McNeer et al.[11] Rosati[30]		Burggraf and Parker[10]		Bruschke et al.[6,7]		Webster et al.[8]		Oberman et al.[9]	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
Single vessel disease												
Normal LV function	29	97	47	95								
Abnormal LV function	42	93	18	100								
Total	71	94	65	97	101	95	202	95	178	93	46	98
Double vessel disease												
Normal LV function	34	94	50	100								
Abnormal LV function	101	87	26	82								
Total	137	90	76	91	86	86	233	80	177	79	50	74
Triple vessel disease												
Normal LV function	37	90	59	87								
Abnormal LV function	162	86	98	76								
Total	200	88	157	82	48	72	118	66	114	63	52	67
Total group												
Normal LV function	102	94	156	94								
Abnormal LV function	306	88	142	81								
Total	408*	90	298	88	235	87	553	82	469	82	148	80

*Excluded from this analysis are 53 patients wtih left main coronary lesions and 46 patients with insufficient data to permit accurate categorization.

LV = left ventricular; no. = number of patients; % = percent surviving.

patients studied by the five centers (1,703 cases), the overall survival rate is also somewhat lower than that reported by the Cooperative Study: 83 percent compared with 90 percent.

Several factors could account for these differences. Because we had noted a distinctly adverse effect of left main coronary arterial lesions on mortality in three vessel disease, for purposes of this analysis we excluded patients with left main coronary disease. Presumably they were included in the other studies. Since left main coronary disease is usually categorized with three vessel disease, this could account for a higher mortality rate in patients with triple coronary disease. If one includes left main lesions, the Cooperative Study 2 year mortality rate for three vessel disease becomes 84 percent; and for the Veterans Administration study as a whole, 88 percent. An additional factor is the incidence and degree of abnormality of left ventricular function, which will adversely affect mortality and is not clearly delineated in most of these studies. Finally, in some of the other studies, selection of patients for nonsurgical treatment may have had a potent although indeterminate effect on prognosis.

Despite these differences, there is reasonably good agreement in the six studies summarized in Table XII upon the following points: (1) single vessel disease is associated with a low 2 year mortality (approximately 5 percent); (2) the mortality is greater in patients with two or three vessel disease; and (3) abnormal left ventricular function is an important factor that increases mortality in subgroups with two and three vessel disease. It should be pointed out that the present data report survival only for a 2 and 1/2 year period. More significant differences may emerge as data are accumulated over a 5 year follow-up period.

Preliminary results of treatment: In keeping with the policy of most soundly designed collaborative clinical trials, treatment results in the Veterans Administration Cooperative Study were kept confidential until one or the other treatment proved to be superior by statistical and clinical standards. During the recruitment phase, confidentiality was held to be essential to prevent conscious or unconscious bias in the assessment of eligibility of patients for inclusion into the study. During the follow-up phase, confidentiality was felt to be most desirable to avoid premature individual decisions about treatment changes. In accordance with this philosophy, the Veterans Administration Study Group published the first treatment results in a recent report on patients with significant left main coronary artery disease.[1] The results showed that in the 53 medically treated patients in this subgroup, the survival rate at 30 months was 65 percent, whereas in the 60 surgically treated patients the corresponding survival rate was 85 percent, a significant difference ($P < 0.025$).

It is expected that in subgroups of patients with early mortality rates lower than those of patients with left main coronary disease, beneficial results with surgery, if they exist, would emerge much later in the follow-up period. Preliminary analysis of the data do not support the view that coronary arterial surgery improves survival in patients with single, double or triple vessel coronary artery disease who have normal left ventricular function. A longer follow-up time will be necessary to delineate more clearly the effect of surgery on longevity not only in these subgroups but also in patients with triple vessel disease and abnormal left ventricular function. Statistically significant trends have not emerged in any of the subgroups of patients so far studied.

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Coronary Arterial Surgery in Patients With Incapacitating Angina Pectoris and Myxedema

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Patients with severe angina pectoris and untreated myxedema pose a clinical dilemma because angina may be exacerbated by thyroid hormone replacement therapy, the usual medical management of angina may be ineffective or even dangerous and invasive diagnostic procedures (cardiac catheterization) and surgery have generally been thought to be contraindicated in myxedema. Because of incapacitating progressive angina refractory to medical management, six patients (mean age 58 years) with severe hypothyroidism (mean serum thyroxine level 0.66 μg/100 ml, normal 4 to 11) underwent selective coronary angiography and quantitative biplane left ventriculography. All patients tolerated cardiac catheterization without complication. Five of the six patients had 70 percent or greater stenosis in three coronary vessels, including three patients with left main coronary artery disease. Coronary revascularization was recommended to each patient. One patient refused surgery and subsequently died suddenly. Another patient was scheduled for elective surgery but in the interim died of a massive acute anterior infarction. Four patients underwent saphenous vein bypass grafting to a mean of 2.8 vessels without complication. Preoperative thyroid hormone replacement ranged from 0 to 50 μg of L-thyroxine daily. Postoperatively adequate thyroid hormone replacement was administered to all patients without complication. At follow-up, a mean of 18 months postoperatively, each of the four operative patients is euthyroid, and all have noted either complete resolution or marked amelioration of their angina. It is concluded that (1) patients with incapacitating angina and myxedema often have severe coronary artery disease; (2) cardiac catheterization can be performed safely in the absence of thyroid replacement; (3) coronary revascularization surgery can be performed safely with minimal thyroid replacement; (4) full thyroid replacement can be safely achieved during the postoperative period.

The management of angina pectoris in the patient with myxedema is a difficult clinical problem. Keating et al.,[1] reviewing the records of 1,503 consecutive patients with myxedema, found 112 patients with the anginal syndrome. Three fourths of these patients had angina before thyroid hormone replacement therapy and the remainder had angina after the institution of therapy. Although thyroid hormone replacement occasionally will alleviate the angina of a patient with myxedema, Smyth[2] has warned of the danger of such replacement in patients with coronary insufficiency and has described patients who sustained a myocardial infarction shortly after therapy was begun. When angina occurs after the initiation of replacement therapy, the achievement of appropriate thyroid hormone replacement is often prevented. Thus, coronary arterial bypass surgery may provide a more rational therapeutic approach to this combination of diseases. After successful coronary revascularization the myxedematous patient might better tolerate full and adequate thyroid replacement.

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It is unclear whether cautious thyroid replacement therapy should precede cardiac catheterization and coronary surgery because of the known propensity of the severely myxedematous patient toward cardiovascular collapse and severe respiratory depression after usual therapeutic doses of narcotic analgesics, sedatives and tranquilizers.[3] This report describes six patients with myxedema and angina pectoris who are presented in an attempt to develop a successful approach to cardiovascular diagnosis and surgical intervention in the myxedematous patient.

Methods

Assay techniques: Serum thyroxine concentrations were measured with the method of Murphy and Jachan[4] (normal range 4 to 11 μg/100 ml). Serum thyrotropin concentrations were determined with radioimmunoassay[5] (normal less than 10 μu/ml).

Cardiac catheterization: Patients were premedicated with intramuscular injections of 50 mg of Phenergan® and 0.6 mg of atropine approximately 90 minutes before catheterization. Right and left heart catheterization was performed with standard techniques, and forward cardiac output was measured with the Fick principle.[6] Oxygen content of the pulmonary and systemic arterial blood samples was determined manometrically with the Van Slyke and Neill method.[7] After the hemodynamic measurements, all patients underwent selective coronary arteriography with the Judkins technique[8] and biplane cine or large film left ventricular angiography. Quantitative angiographic volume measurements were performed using the area-length method of Dodge et al.[9] In our laboratory, normal values have been established as follows: cardiac index 2.5 to 4.2 liters/min per m^2, arteriovenous oxygen difference 5 ml/100 ml or less, oxygen consumption 125 ml/min per m^2, ejection fraction 0.61 ± 0.07 (standard deviation), left ventricular end-diastolic volume 76 ± 15 ml/m^2 and end-systolic volume 30 ± 9 ml/m^2.

Case Histories

Patient 1: This 52 year old white man was admitted to the hospital in August 1973, for evaluation of incapacitating chest pain. In 1962, he had sustained an anterior myocardial infarction and in 1963, had undergone therapeutic thyroid ablation with 25 μCi of iodine-131 for intractable angina. His angina was relieved for only a few months. In the 2 years before admission, he had become profoundly myxedematous but was able to tolerate only 15 mg of thyroid USP daily because of increasing chest pain. He was intolerant of nitroglycerin, which produced severe hypotension and syncope on three occasions.

Physical examination revealed an obviously hypothyroid white man who was normotensive with a regular pulse of 48/min. There was no jugular venous distension or thyromegaly. The lungs were clear, and no abnormal heart sounds or murmurs were heard. There was no peripheral edema, and all deep tendon reflexes had a greatly delayed recovery. The admission electrocardiogram revealed sinus bradycardia, right bundle branch block and an old anteroseptal infarction with persistent S-T elevation. Cardiac X-ray series and fluoroscopy showed moderate enlargement of the left ventricle, pulmonary venous congestion and calcification in the left main, left anterior descending, left circumflex and right coronary arteries. Serum thyroxine was 0.5 μg/100 ml (Table I).

The patient underwent cardiac catheterization without difficulty or complication. The hemodynamic data are presented in Table II. Coronary arteriograms revealed severe three vessel coronary artery disease including 70 percent stenosis of the luminal diameter of the left main coronary artery. In October 1973, he underwent three vessel saphenous vein grafting. His immediate postoperative cardiac index was 1.0 liter/min per m^2, and he was given intravenously administered digoxin (1.25 mg over 24 hours) and epinephrine (3.2 μg/min). On the first postoperative day oral administration of 15 mg/day of thyroid USP was begun. By the third postoperative day he no longer required pressor agents, and his cardiac index had risen to 1.9 liters/min per m^2, as measured with the indicator-dilution method using indocyanine green. There was no apparent perioperative myocardial infarction. The remainder of the hospital course was uncomplicated and he was discharged on a regimen of digoxin 0.25 mg, Lasix 40 mg and thyroid USP 15 mg daily.

The patient was readmitted 1 year later for reevaluation. He was clinically and chemically euthyroid (serum thyrotropin 9.4 μu/ml) with a dose of 75 μg of L-thyroxine daily, and he reported a decrease in angina. Use of digitalis and a diuretic agent had previously been discontinued, and he complained of only mild dyspnea on exertion. When seen 2 1/2 years after operation, he had stable exertional angina with one episode a week and was walking 0.8 km three times a week.

Patient 2: This 58 year old white woman was admitted in September 1973 for evaluation of dull retrosternal chest pain of 5 years' duration. She had not sought medical attention until March 1971, when she was found to have hypertension, hypercholesterolemia and an "abnormal electrocardiogram." Treatment with antihypertensive agents, clofibrate and nitrates was started and she did well until May 1973, 4 months before the present admission, when she noted increasing fre-

TABLE I

Clinical and Angiographic Data

Case no.	Age (yr) & Sex	T4	Chol	TG	Coronary Vessels With 70 Percent Stenosis	Surgery
1	52 M	0.5	259	154	LMCA,LAD,LCx,RCA	3V SVG
2	58 F	0.5	246	302	LMCA,LAD,RCA	Died (refused)
3	62 M	1.0	269	333	LAD,RCA,LCx (dom)	2V SVG
4	46 M	0.6	468	321	LAD,RCA	2V SVG
5	66 F	0.6	331	325	LMCA,LAD,LCx,RCA	4V SVG
6	64 M	0.8	356	429	LAD,LCx,RCA	Died (before surgery)

Chol = serum cholesterol (mg/100 ml); dom = dominant coronary artery; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LMCA = left main coronary artery; RCA = right coronary artery; SVG = saphenous vein graft surgery; T4 = serum thyroxine (μg/100 ml); TG = serum triglyceride (mg/100 ml); V = vessel.

TABLE II

Hemodynamic and Quantitative Left Ventriculographic Data

Case no.	PCP (mm Hg)	HR	O_2 Cons	CI	a-v O_2	LVEDV	LVESV	EF	LV Wall Motion	Pericardial Effusion
1	3	60	57	1.06	5.39	101	49	0.45	Apical dyskinesia, inferolateral akinesia	No
2	5	86	96	2.36	4.06	70	35	0.50	Minimal inferior and apical dyskinesia	Yes
3	3	66	79	1.54	5.14	84	47	0.45	Inferoapical akinesia, apical dyskinesia	Yes
4	5	94	100	2.04	4.91	57	24	0.58	Normal contraction	No
5	5	60	98	1.65	5.93	79	48	0.39	Anterior hypokinesia, apical dyskinesia	No
6	4	72	91	2.30	3.95	49	14	0.71	Normal contraction	Yes

a-v O_2 Diff = arteriovenous oxygen difference (ml/100 ml); CI = cardiac index (liters/min per m^2); EF = ejection fraction; HR = heart rate (beats/min); LV = left ventricular; LVEDV = left ventricular end-diastolic volume (ml/m^2); LVESV = left ventricular end-systolic volume (ml/m^2); O_2 Cons = oxygen consumption (ml/min per m^2); PCP = pulmonary capillary wedge pressure (mm Hg).

quency of chest pain. She also reported 4 years of increasing skin dryness, body hair loss and proximal leg weakness.

Physical examination revealed an obese white woman with a deep hoarse voice. She was normotensive with a regular pulse of 72/min. There was no jugular venous distension or thyromegaly. There were bilateral carotid bruits. Lungs were clear. Auscultation revealed a fourth sound gallop. There were trace pedal edema and skin changes of myxedema. The deep tendon reflexes had a delayed recovery and there was marked proximal muscle weakness. Serum thyroxine was 0.5 μg/100 ml and serum cortisol levels were normal. Electrocardiogram showed minor nonspecific T wave changes. Cardiac X-ray series and fluoroscopy revealed slight cardiac enlargement and calcification in the left main coronary artery. Echocardiogram indicated pericardial effusion posteriorly.

The patient received three daily doses of 7.5 mg of thyroid USP before undergoing cardiac catheterization which was uneventful (Table II). Coronary arteriograms showed severe stenosis of the left main (90 percent stenosis), left anterior descending and dominant right coronary arteries. The patient refused surgical intervention. On the day after cardiac catheterization, angina developed and she died suddenly. Autopsy permission was refused.

Patient 3: This 62 year old white man was admitted to the hospital in July 1974 for evaluation of choking left parasternal pain of 15 years' duration. He was hospitalized on three occasions during the preceding 3 years because of angina, dyspnea and ankle edema; myocardial infarction was not documented. His symptoms had continued to progress and he complained of two to three episodes of chest pain daily occurring at rest, orthopnea and paroxysmal nocturnal dyspnea. In addition, during the last 3 years, he had noted onset of cold intolerance, hoarseness, generalized muscle weakness, coarsening of body hair and constipation.

Physical examination revealed an obese man with puffy eyelids, delayed movements, slow mentation and a very hoarse voice. He was normotensive with a regular pulse of 68/min. There was no jugular venous distension or thyromegaly. The lungs were clear, and percussion of the chest revealed apparent cardiomegaly. The apex impulse was not felt, and no abnormal sounds or murmurs were appreciated. There was trace pedal edema. All deep tendon reflexes were diminished. Marked proximal muscle weakness was noted. Serum thyroxine was 1.0 μg/100 ml and serum thyrotropin was 115 μu/ml. The chest X-ray film revealed cardiomegaly and venous congestion. The electrocardiogram showed diffuse S-T changes and T wave flattening. The echocardiogram revealed an anterior pericardial effusion. The patient was believed to have severe angina pectoris and myxedema. It was elected to proceed with coronary arteriograms before instituting thyroid hormone replacement therapy.

Cardiac catheterization was performed without difficulty (Table II). Coronary arteriograms revealed a left dominant system with greater than 70 percent stenosis in both the left anterior descending and left circumflex arteries and total occlusion of the nondominant right coronary artery.

Therapy was begun with 25 μg of L-thyroxine daily for 2 weeks, then the dose was increased to 50 μg daily. The patient noted marked improvement in strength and mentation; however, his angina again became progressively worse but it again stabilized with the institution of long-acting nitrates. In late October 1974 the patient underwent saphenous vein bypass grafting to the left anterior descending and left circumflex coronary arteries without complication. The immediate postoperative cardiac index was 1.4 liters/min per m^2 but rose 2 hours later to 1.7. On the first postoperative day, L-thyroxine was resumed at 50 μg daily and on the seventh day the dose was increased to 75 μg daily. There was no apparent perioperative myocardial infarction, and the postoperative recovery was uneventful except for premature ventricular contractions controlled with orally administered procainamide. The patient was discharged angina-free on a regimen of procainamide, L-thyroxine and a diuretic drug.

At follow-up 2 years later, he was receiving 200 μg of L-thyroxine daily and was clinically euthyroid. He had resumed full activity, including gardening and riding a bicycle, without angina.

Patient 4: This 46 year old white man was admitted to the hospital in April 1975 for evaluation of "chest tightness" of 5 months' duration occurring with exercise and immediately relieved by sublingually administered nitroglycerin. He also complained of several years of decreasing strength and libido, coarsening of his skin and body hair and deepening of his voice.

Physical examination revealed slow mentation, a hoarse voice and obvious skin changes of myxedema. He was nor-

motensive and his pulse 60/min and regular. There was no jugular venous distension or thyromegaly. The lungs were clear. No abnormal heart sounds or murmurs were heard. The deep tendon reflexes revealed a markedly delayed relaxation phase. Serum thyroxine was 0.6 μg/100 ml and serum thyrotropin was greater than 100 μu/ml. The chest X-ray film was normal, and the electrocardiogram revealed only nonspecific ST-T changes.

Cardiac catheterization (Table II) was performed before thyroid hormone replacement therapy and was uncomplicated. Coronary arteriograms revealed more than 70 percent stenosis of both the left anterior descending and the dominant right coronary arteries. The patient received 50 μg of L-thyroxine daily for 2 days before undergoing two vessel saphenous vein bypass grafting, which was uncomplicated. On the first postoperative day, administration of 50 μg of L-thyroxine daily was resumed. Routine electrocardiogram 1 week postoperatively revealed anteroseptal changes suggestive of infarction but the patient had had no chest pain since his operation. Enzyme determinations were not performed, and there were no hemodynamic changes. After discharge, the patient successfully received full thyroid hormone replacement over a 2 month period.

At follow-up, 1 year later, the patient is clinically and chemically euthyroid and has returned to full activity without angina.

Patient 5: This 66 year old hypertensive diabetic white woman was admitted to the hospital in September 1976 for evaluation of incapacitating chest pain. The pain had started in 1969, but in recent months its frequency and severity had increased and she had become bedridden. Propranolol therapy produced a mild reduction in her chest pain, although bradycardia to 50/min was produced by doses of more than 5 mg four times a day. She also reported having dryness of skin and hair and decreased memory and hearing of several months' duration.

Physical examination revealed an obese woman with facies, skin and hair suggestive of myxedema, blood pressure of 170/80 mm Hg and pulse of 64/min and regular. There was no jugular venous distension or thyromegaly. The lungs were clear. There was a grade 1/6 systolic ejection murmur at the apex and base. There was no pedal edema. The relaxation phase of the deep tendon reflexes was prolonged.

Laboratory data revealed a serum thyroxine of 0.6 μg/100 ml and serum thyrotropin of more than 100 μu/ml. Electrocardiogram revealed left axis deviation and probable old anterior infarction. Cardiac fluoroscopy showed calcium in the aorta, aortic valve and coronary arteries.

The patient had cardiac catheterization without complication (Table II). There was no pressure gradient across the aortic valve. Coronary angiography showed more than 70 percent stenosis of the left main, left anterior descending, left circumflex and right coronary arteries.

Without thyroid replacement, the patient underwent saphenous vein bypass grafting to the left anterior descending, right coronary artery, first diagonal branch of the left anterior descending artery and first marginal branch of the circumflex artery. Her immediate postoperative cardiac index was 1.7 liters/min per m^2, and she was given a bolus injection of 200 μg L-thyroxine intravenously. On the first postoperative day, a regimen of 15 mg of thyroid USP by mouth daily was begun. Her postoperative course was entirely uncomplicated except for premature ventricular contractions controlled with quinidine. Before discharge the thyroid supplement was increased to 30 mg daily without recurrence of angina.

At follow-up 6 months postoperatively, the patient was euthyroid on 120 mg of thyroid USP daily and was at full activity, walking 3.2 km daily without angina.

Patient 6: This 64 year old white man was admitted in November 1976 for evaluation of cramping chest pain of 2 months' duration. For the past 10 years he had taken 60 mg of thyroid USP sporadically for symptoms of weight gain, dry scaly skin, hoarseness and facial puffiness. One week before admission he underwent graded exercise testing at another hospital. At 3 minutes of exercise, numerous premature ventricular beats developed in association with nondiagnostic S-T changes, and the test was terminated. Immediately after exercise, he had ventricular tachycardia with loss of consciousness and electrical cardioversion was required. There was no myocardial necrosis after the episode.

On admission, the pulse was 64/min and regular, and blood pressure 124/84 mm Hg. There was no jugular venous distension or thyromegaly. The lungs were clear of rales, and no cardiac murmurs or gallop sounds were detected. There was no peripheral edema and all deep tendon reflexes were normal. The admission electrocardiogram showed minor nonspecific ST-T abnormalities; the cardiac X-ray series was normal. Serum thyroxin was 0.8 μg/100 ml (Table I).

The patient underwent cardiac catheterization without difficulty (Table II). Coronary arteriograms revealed severe proximal three vessel coronary artery disease. Treatment was begun with isosorbide dinitrate, 5 mg every 3 hours sublingually, and propranolol, 20 mg four times a day. On this regimen angina ceased and the heart rate decreased to 60/min. The patient was then cautiously given 25 μg of L-thyroxine daily and he tolerated this dose without exacerbation of angina. In view of the severity of his coronary artery disease with normal left ventricular function, he was scheduled for elective saphenous vein bypass grafting and discharged. Two weeks after discharge, he began to have angina at rest. One week later after a prolonged episode of chest pain, he was readmitted to the hospital with an acute anterior myocardial infarction and cardiogenic shock. Shortly after admission, he had a cardiopulmonary arrest and could not be resuscitated. Postmortem examination documented severe three vessel coronary artery disease and a fresh anterior apical infarction.

Discussion

Angina pectoris is not a rare problem in the patient with myxedema.[1] Thyroid hormone replacement will increase heart rate, myocardial contractility and myocardial oxygen consumption and may result in worsened angina or myocardial infarction. Therefore, adequate thyroid hormone replacement is often unattainable in the myxedematous patient whose angina has not responded optimally to medical management. In such patients, successful coronary arterial revascularization may make adequate therapy of hypothyroidism possible. This report describes six patients with untreated or suboptimally treated myxedema and severe coronary artery disease, four of whom subsequently underwent successful saphenous vein bypass grafting and adequate thyroid replacement.

Cardiac Catheterization

In the precatheterization evaluation of a myxedematous patient, routine laboratory data may be misleading. Secondary to reduced enzyme clearance, an elevation of serum creatine kinase may be noted, but

isoenzyme analysis confirms its source as skeletal muscle.[10] The electrocardiogram can also be confusing, showing inverted T waves, delayed conduction,[11] complete heart block[12] and prolonged Q-T interval,[13] suggesting ischemic disease or electrolyte imbalance. These changes usually revert to normal with adequate thyroid hormone replacement.

Hemodynamic data observed in hypothyroid patients have been reported.[14,15] Typically, the cardiac index and oxygen consumption are decreased whereas arteriovenous oxygen difference is normal. Repeat determinations after adequate thyroid hormone replacement document normalization of the cardiac index and oxygen consumption. However, severe left ventricular dysfunction secondary to hypothyroidism is uncommon, and when congestive heart failure occurs in myxedema there is usually concomitant primary heart disease.[16]

In the present series, all patients were markedly hypothyroid, but only three (Patients 1, 3 and 5) demonstrated abnormal left ventricular ejection fraction, and two of these (Patients 1 and 5) had electrocardiographic evidence of antecedent myocardial infarction. Evidence for significant left ventricular myocardial depression secondary to myxedema was thus lacking in the majority of our patients.

Clinical Management of the Myxedematous Patient With Angina

The mainstays of medical management of angina pectoris are nitroglycerin, long-acting nitrates and the beta adrenergic blocking agent, propranolol. Unfortunately, these agents may prove ineffective and even dangerous in the setting of myxedema.

Nitrates: Patient 1 had multiple episodes of hypotension and syncope after sublingual administration of nitroglycerin. This exaggerated vasodilator response might be secondary to the reduced total blood and plasma volumes seen in myxedema.[15] Long-acting nitrates were used in five of our patients and were of some symptomatic benefit. However, the amelioration of angina was not sufficient to allow adequate thyroid replacement in any case.

Propranolol: In light of the beneficial effects of propranolol in hyperthyroidism, a combination of thyroid hormone replacement and propranolol might seem a rational means of treating the myxedematous patient with coronary artery disease. However, thyroid hormone has an apparent direct chronotropic and inotropic effect on the heart that is not blocked by propranolol.[17] Steinberg and Schrader,[18] despite the use of propranolol, could not increase the triiodothyronine dose above 7.5 μg daily without severely exacerbating the angina of a 60 year old man with myxedema and extensive diffuse coronary artery disease. In addition, beta adrenergic blockade may not be well tolerated in the severely hypothyroid patient. In our series, Patient 5 had received propranolol before thyroid hormone replacement, but the dose could not be increased above 5 mg four times a day because of marked bradycardia. Patient 6 also received long-acting nitrates and propranolol before thyroid hormone replacement therapy. Initially he tolerated thyroid replacement well; however, in the third week of treatment he had progressive angina with subsequent massive myocardial infarction and death.

Coronary arterial surgery: In view of the inadequacies of current medical management, we chose to offer surgical intervention to each of our hypothyroid patients before full thyroid hormone replacement had been achieved. This decision was substantiated by the finding of severe coronary artery disease in all six patients, three of whom had left main coronary arterial lesions. Surgical intervention in these latter three patients was performed in light of the improved survival rates in patients with surgically treated left main coronary artery disease.[19]

It is still a matter of conjecture whether minimal thyroid replacement should be begun before coronary arterial surgery. Cardiac glycogen stores have a protective effect in the anoxic arrested heart[20]; however, McDaniel et al.[21] described a defect in muscle glycogen breakdown and lactate release in response to an ischemic stimulus in the untreated hypothyroid patient. The defect was reversed when thyroid hormone replacement was begun. The untreated myxedematous patient is also prone to intraoperative cardiovascular collapse, severe respiratory depression, infection, adynamic ileus and an inappropriate antidiuretic hormone-like syndrome.[22] These possibilities must be weighed against the real danger of myocardial infarction preoperatively when thyroid hormone replacement is begun.

Nelson et al.[23] reported on two patients with myxedema who underwent coronary bypass surgery. The first patient received no thyroid supplement preoperatively, and his operative course was complicated by inappropriate antidiuretic hormone-like syndrome, severe adynamic ileus and infection; the second patient received 10 μg of triiodothyroxine daily preoperatively and did well postoperatively on 200 μg of L-thyroxine daily.

In our series, three patients received doses of less than 50 μg of L-thyroxine replacement before operation, and one patient received no thyroid hormone preoperatively. All four patients had no apparent intraoperative difficulty, and in the immediate postoperative periods those who had received preoperative thyroid hormone were continued on small but increasing doses of hormone, whereas the patient operated on without prior thyroid hormone replacement received 200 μg of L-thyroxine at the completion of operation and 15 mg of thyroid daily.

Our experience therefore suggests that the patient with myxedema and severe angina might be successfully managed with minimal thyroid replacement (0 to 50 μg L-thyroxine daily) preoperatively with gradual but more aggressive thyroid replacement in the early postoperative period. According to a recent report,[24] oral thyroid replacement will begin to improve myocardial performance only when replacement therapy reaches an equivalent of 50 to 75 μg of thyroxine daily.

Each of the surgically managed patients experienced dramatic diminution of angina postoperatively. Objective pre- and postoperative assessment of angina

threshold with graded exercise testing would have been useful but was precluded by the unstable angina present in most patients. The mechanisms for production of angina and its relief by coronary revascularization surgery[25] are still controversial. Amelioration of angina in one of our four operative patients (Patient 4) might have been secondary to intraoperative or "silent" postoperative myocardial necrosis.

Clinical implications: Further controlled clinical studies are indicated to assess the relative merits of medical versus surgical treatment of angina in patients with myxedema and severe coronary artery disease. Future studies should employ larger numbers of patients, with longer follow-up periods, postoperative arteriography to assess graft patency and, optimally, objective pre- and postoperative assessment of angina threshold, myocardial blood flow and thyroid status, employing graded exercise testing, myocardial scintigraphy and measurement of appropriate biochemical variables.

Our study clearly shows that patients with myxedema and severe angina have a great tendency to have severe proximal coronary artery disease, including left main coronary artery disease. Their condition should therefore be regarded as highly unstable, although our experience suggests that cardiac catheterization and coronary arterial surgery can be successfully performed in the absence of significant thyroid replacement. If thyroid replacement is administered preoperatively, we recommend that it be given only to patients remaining in the hospital under a physician's observation. Complete thyroid replacement can be effectively administered in the postoperative period after successful coronary revascularization surgery.

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Hemodynamic Benefits of Atrioventricular Sequential Pacing After Cardiac Surgery

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The hemodynamic effects of atrioventricular (A-V) sequential pacing were assessed and compared with those of ventricular and of atrial pacing in 10 patients with and without heart block after cardiac surgery. Ventricular pacing alone was either hemodynamically detrimental or of no benefit in six of the eight patients who initially had sinus or accelerated junctional rhythms. Atrial pacing alone produced significant improvement in cardiac output in all patients who were not pacemaker-dependent. However, five of the eight patients with intact A-V conduction had further increases in cardiac output through A-V sequential pacing at shorter than intrinsic A-V intervals. Optimal A-V intervals for maximal cardiac output could be identified in all patients and varied widely. Significant changes in cardiac output occurred with relatively small deviations in the A-V interval. In selected patients after cardiac surgery, temporary A-V sequential pacing is a workable and valuable adjunctive form of hemodynamic support and is preferable to ventricular or atrial pacing.

The importance of a properly timed atrial systole in the maintenance of optimal cardiac output, particularly in the abnormal heart, is well recognized.[1–5] When an appropriate atrial contraction precedes ventricular systole, augmented ventricular filling may result in greater stroke volume in response to increased diastolic volume and fiber length, thus producing a shift to a more optimal position on the Frank-Starling curve.[6] Inappropriately short atrioventricular (A-V) delay may not enhance cardiac output because of an inadequate time for antegrade atrial emptying before ventricular systole.[4] Excessively long A-V delay may yield no increase in cardiac output or may decrease stroke volume through disordered mitral valve closure, causing "atriogenic mitral reflux."[7,8] During junctional or ventricular rhythms, cardiac output may be significantly reduced despite adequate ventricular rates. In these situations, retrograde conduction may cause less than optimal A-V relations, including simultaneous contraction of the atria and ventricles. When present, A-V dissociation causes a loss of consistent atrial contribution to filling and variable "functional" mitral regurgitation due to random A-V relations.[2,9] Ventricular pacing is analogous to an accelerated idioventricular rhythm and is hemodynamically inferior to atrial pacing.[1,9]

A-V sequential pacing has been used to preserve the A-V relation and has been reported to improve hemodynamics in patients with chronic complete heart block[4] and with heart block complicating myocardial infarction[10] or cardiac surgery.[11] Other benefits attributed to sequential pacing have included simultaneous suppression of atrial and ventricular ectopy,[11,12] more effective control of junctional reentrant tachycardias[11,12] and, possibly, a decrease in myocardial oxygen consumption from the level observed during ventricular pacing at the same rate.[13]

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TABLE I

Summary of Cases

Case no.	Age (yr) & Sex	Surgical Procedure	Postoperative Rhythm: Type	Postoperative Rhythm: Rate/Min	Cardiac Output (liters/min)*
1	43M	Aortic valve replacement	Normal sinus	70	4.95
2	60F	Aortic valve replacement	Junctional	60	3.49
3	51M	Aortic valve replacement	Junctional	80	5.07
4	73F	Aortic and mitral valve replacement	Junctional	79	2.65
5	69F	Aortic and mitral valve replacement	Junctional	62	2.43
6	58F	Aortic valve replacement and mitral valve annuloplasty	Normal sinus	71	2.60
7	46M	Mitral valve replacement	Normal sinus	107	4.07
8	39M	Saphenous vein bypass graft	Normal sinus	84	5.15
9	9M	Correction of type A3 common ventricle	3° A-V block, ventricular pacing	75	2.11
10	17M	Correction of double-outlet right ventricle	3° A-V block, ventricular pacing	120	5.71

*All patients had a resting cardiac index of less than 2.5 liters/min per m^2.

This report describes our initial experience with A-V sequential pacing in 10 patients with and without heart block after cardiac surgery. We compared ventricular, atrial and A-V sequential pacing with particular reference to hemodynamic changes corresponding to different A-V intervals in these subjects.

Material and Methods

The study group consisted of six male and four female patients aged 9 to 73 years (Table I). Operations consisted of isolated aortic valve replacement (three patients), combined aortic and mitral valve replacement or mitral valve annuloplasty (three patients), isolated mitral valve replacement (one patient), aortocoronary bypass grafting (one patient) and repair of a complex congenital heart defect (two patients). One of the last two patients had type A3 common ventricle with preoperative complete heart block and the other had double-outlet right ventricle. Only these two patients with a congenital heart defect had complete heart block postoperatively and were pacemaker-dependent. The remaining eight patients continued to have sinus or accelerated junctional rhythms postoperatively.

Temporary paired atrial and ventricular wires for bipolar pacing were attached at operation and were exteriorized through the chest wall. Sequential pacing was performed with a commercially available bifocal pacemaker (American Optical, Bedford, Massachusetts). Cardiac output was determined with use of a computer after the injection of indocyanine green dye into a transthoracic left atrial catheter, with sampling at the radial artery. All determinations were made within 12 hours of operation.

Cardiac output was determined during resting sinus or junctional rhythm in the eight patients who were not pacemaker-dependent (Table II). All patients had a resting cardiac

TABLE II

Cardiac Output During Ventricular, Atrial and A-V Sequential Pacing at Intrinsic P-R and Optimal A-V Intervals

Case no.	Rate/Min	Ventricular Pacing Output (liters/min)	Atrial Pacing: Output (liters/min)	Atrial Pacing: P-R Interval (msec)	Sequential A-V Pacing: Output (liters/min)	Sequential A-V Pacing: Optimal A-V Interval (msec)
1	90	3.95	5.40	180	5.65	150
2	75	3.90	5.79	250	6.52	150
3	100	5.13	6.48	220	6.78	150
4	95	2.70	3.20	240	. . .	*
5	100	2.99	3.20	280	4.24	250
6	100	2.46	2.89	250	. . .	*
7	120	3.0	3.69	240	5.01	200
8	100	4.3	5.55	200	. . .	*
9	75	2.11	. . .	. . .	2.49	50
10	120	5.71	. . .	. . .	7.52	100

*A-V intervals shorter than the intrinsic P-R interval resulted in decreasing cardiac output.

index of less than 2.5 liters/min per m^2. Subsequently, an atrial rate between 75 and 120/min was selected that allowed continuous atrial capture. This basic pacing rate was not changed while cardiac output was determined during atrial pacing alone, ventricular pacing alone and sequential pacing at A-V intervals of 25 to 250 msec. The intrinsic A-V conduction ability of the eight patients who were not pacemaker-dependent determined the maximal A-V interval. For purposes of comparison, we considered paced A-V intervals identical with intrinsic P-R intervals to be equivalent. Because of a Mayo Clinic policy limiting reinfusion of blood withdrawn for cardiac output determinations, in most patients it was judged not feasible to repeat output determinations at each setting. However, when output determinations were repeated, the results were averaged.

Results

Ventricular pacing was hemodynamically detrimental in all four patients who originally had sinus rhythm (Fig. 1), and the pacing rate ranged from 13 to 29/min greater than the rate during sinus rhythm.

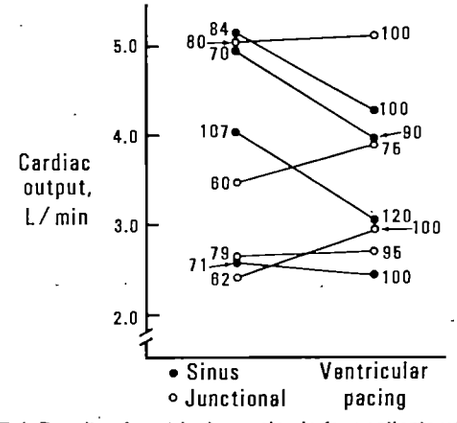


FIGURE 1. Results of ventricular pacing in four patients who initially had sinus rhythm **(closed circles)** and four who initially had accelerated junctional rhythms **(open circles)**. Resting heart rates are shown at **left** and ventricular paced rates at **right**. L = liters.

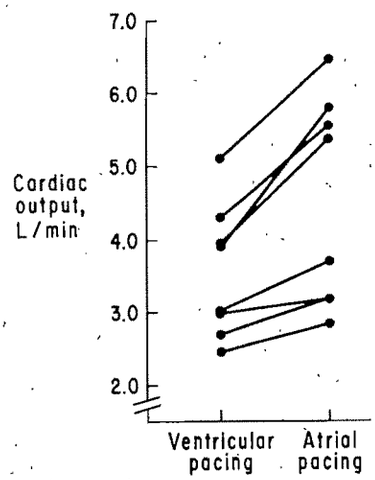


FIGURE 2. Results of atrial and ventricular pacing at identical heart rates in eight patients who were not pacemaker-dependent.

Ventricular pacing increased cardiac output significantly in only two of the four patients who initially had accelerated junctional rhythms (Fig. 1), and the pacing rates ranged from 16 to 38/min greater than the rates during junctional rhythm.

During atrial and A-V sequential pacing, it was possible to identify an optimal A-V or P-R interval that produced maximal cardiac output in all patients. In this small series, the optimal A-V interval did not correlate with the basic pacing rate and varied widely from patient to patient, being as short as 50 msec in a 9 year old child with common ventricle and as long as 250 msec in a 69 year old woman with combined aortic and mitral valve replacement. However, in the eight adult patients with predominant valve disease, the optimal A-V or P-R intervals ranged from 150 to 250 msec.

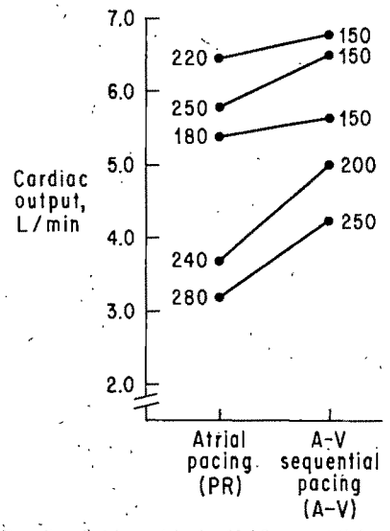


FIGURE 3. Results of atrioventricular (A-V) sequential pacing at shorter A-V intervals compared with results of atrial pacing in five patients with intact A-V conduction. Intrinsic P-R intervals in milliseconds are shown at **left** and A-V paced intervals in milliseconds at **right.**

In eight patients with intact A-V conduction, atrial pacing alone produced an increase in cardiac output for an overall mean increase of 26 percent ($P < 0.001$) over that during ventricular pacing alone (Fig. 2). This improvement in cardiac output ranged from 7 to 49 percent, the greatest percent increases occurring in two patients with isolated aortic valve disease (Cases 1 and 2).

In five of the eight patients with intact A-V conduction (Cases 1, 2, 3, 5 and 7), further increases in cardiac output were obtained by artificially shortening the A-V interval beyond that attained with atrial pacing alone (Fig. 3). Cardiac output increased by a mean of 18 percent ($P < 0.05$, range 5 to 36 percent) from the value during atrial pacing, and by a mean of 50 percent ($P < 0.01$, range 32 to 67 percent) from the value during ventricular pacing alone. In the remaining three patients with intact A-V conduction (Cases 4, 6 and 8), the intrinsic P-R interval was optimal, and shorter A-V intervals reduced cardiac output to less than that achieved with atrial pacing. When the entire group of 10 patients was considered, A-V sequential pacing increased cardiac output by a mean of 34 percent ($P < 0.001$, range 2 to 67 percent) over the value obtained during ventricular pacing alone.

Case 9: Results obtained in this 9 year old boy who underwent repair of type A3 common ventricle complicated by complete heart block are shown in Figure 4. At the end of operation and attempted termination of cardiopulmonary bypass, the arterial systolic pressure was 70 mm Hg with ventricular pacing alone. With the addition of A-V sequential pacing, the systolic pressure increased to 90 mm Hg. While the patient was in the postoperative intensive care unit, the optimal A-V interval was very short (50 msec), resulting in an increase of 18 percent in cardiac output compared with that during ventricular pacing at the same rate. Longer A-V intervals caused a decrease in cardiac output, and an A-V interval of 200 msec caused cardiac output to decrease to less than the value achieved with ventricular pacing alone.

Case 5: Results obtained in this 69 year old woman who underwent combined aortic and mitral valve replacement are

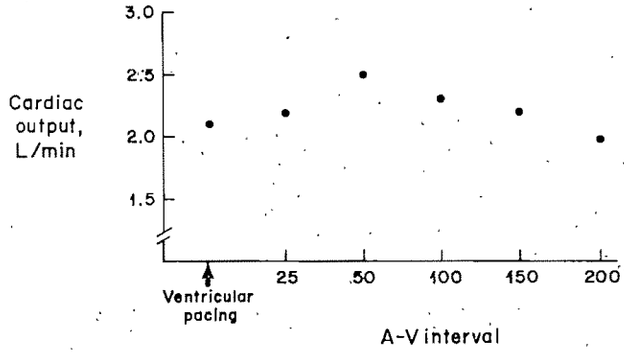


FIGURE 4. Case 9. A 9 year old boy with type A3 common ventricle and complete heart block. All pacing was performed at a rate of 75/min. Cardiac output during ventricular pacing was 2.11 liters/min. Output (in liters/min) during A-V sequential pacing was 2.21 at an A-V interval of 25 msec, 2.49 at 50 msec, 2.29 at 100 msec, 2.19 at 150 msec and 1.97 at 200 msec.

shown in Figure 5. In the postoperative intensive care unit, she had a junctional rhythm with a rate of 62/min and cardiac output of 2.43 liters/min (cardiac index 1.63 liters/min per m^2). Ventricular pacing alone at 100 beats/min increased the cardiac output to 2.99 liters/min. Atrial pacing alone at the same rate produced a P-R interval of 280 msec and increased further the cardiac output to 3.2 liters/min. However, A-V sequential pacing at a shorter A-V interval of 250 msec maximized cardiac output at 4.24 liters/min, for an increase of 33 percent. This record illustrates that relatively small deviations from the optimal A-V interval can produce significant changes in cardiac output.

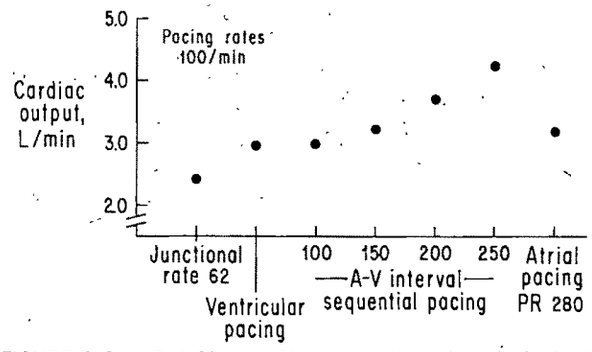


FIGURE 5. Case 5. A 69 year old woman with aortic and mitral valve replacement. Postoperative junctional rate was 62/min and cardiac output was 2.43 liters/min. All pacing was performed at 100/min. Cardiac output (liters/min) was as follows: ventricular pacing alone, 2.99, atrial pacing alone, 3.2 (P-R interval 280 msec); A-V sequential pacing, 3.02 at an A-V interval of 100 msec, 3.24 at 150 msec, 3.72 at 200 msec and 4.24 at 250 msec.

Discussion

Cardiac surgeons often use temporary ventricular pacing to maintain adequate heart rate and cardiac output postoperatively. However, previous investigators[3] have reported that stepwise increases in ventricular pacing rate produce a progressive decrease in cardiac output in patients with compensated heart disease. As expected, ventricular pacing alone failed to improve hemodynamics in six of our eight patients who originally had sinus or accelerated junctional rhythms. At increased ventricular pacing rates (mean increase 21/min), cardiac output either decreased or demonstrated insignificant change.

The atrial contribution to stroke volume and cardiac output in the normal heart has been reported to be between 15 and 20 percent.[14] In our series, atrial pacing alone increased cardiac output by 26 percent and A-V sequential pacing increased it by 34 percent, thus emphasizing the importance of atrial systole in the abnormal heart after cardiac surgery. Our observations and those of others[15] suggest that the hypertrophied poorly compliant ventricle may benefit greatly from the atrial contribution to filling and A-V sequential pacing. These data suggest that in many postoperative patients ventricular pacing alone is not the preferable mode of temporary pacing.

The optimal A-V interval: Uncertainty exists regarding the proper A-V interval.[16] The electric A-V interval may not equal the mechanical A-V interval because of dissimilar electromechanical delays within the atria and ventricles, differing positions of pacing electrodes and intraatrial or intraventricular conduction delays. Leinbach et al.[4] and Chamberlain et al.[10] found that the optimal A-V interval was 150 msec in patients with chronic complete heart block and 100 msec or less in patients with heart block complicating acute myocardial infarction. They speculated that this difference might reflect effects of heart rate or delay in left ventricular mechanical events during right ventricular pacing.

In our series of patients with A-V sequential pacing after cardiac surgery, the determination of an optimal A-V interval was critical to the maintenance of maximal cardiac output. Adults required intervals that ranged from 150 to 250 msec, whereas two younger patients (one aged 9 and the other 17 years) with a congenital heart defect required intervals of 50 and 100 msec, respectively. Deviation from the optimal A-V interval by less than 50 msec reduced the cardiac output by as much as 33 percent in individual patients.

There was no apparent relation between heart rate and optimal A-V interval despite the observation by others[14] that, at faster heart rates, the percent contribution of atrial contraction to cardiac output becomes greater. This finding may reflect the unique hemodynamics of the postoperative patient or the particular underlying cardiac lesion. These factors plus the heterogeneity of patients studied do not allow us to make meaningful observations regarding the relation of heart rate and A-V interval.

Therapeutic implications: High grade heart block need not be present for patients to benefit hemodynamically from A-V sequential pacing. Five patients with intact A-V conduction had 1:1 conduction and P-R intervals ranging from 180 to 260 msec during sinus rhythm or atrial pacing. However, artificial shortening of the P-R or A-V interval through sequential pacing augmented cardiac output by a mean of 18 percent over that obtained during atrial pacing alone. Consequently, A-V sequential pacing might be considered an adjunctive or alternative method of hemodynamic support for selected postoperative patients even in the absence of heart block or impaired A-V conduction. Theoretically, this increased cardiac output might be achieved at lesser myocardial oxygen cost[11,17] than that achieved through administration of inotropic agents.

A-V sequential pacing is not the pacing technique of choice for all postoperative patients. It cannot be performed reliably in a large group of patients with persistent atrial tachycardias, flutter and fibrillation because atrial capture is not possible under these circumstances. Many patients receiving infusions of sympathomimetic amines postoperatively do not benefit hemodynamically from sequential pacing because of the high pacing rates required for consistent atrial capture. However, temporary A-V sequential pacing can be utilized to improve postoperative hemodynamics in selected patients with or without heart block.

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Clinical Use of A New Transvenous Atrial Lead

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A new atrial lead has been developed for permanent cardiac pacing and implanted in 53 patients. This lead has a premolded distal J portion containing an arrangement of nine pliant tines intended to effect fixation in the trabeculations found in the right atrial appendage. Eighteen patients received *P* wave synchronous ventricular pacemakers (VAT) for management of complete atrioventricular block and 35 received atrial stimulating pacemakers (AAT or AAI) for the management of sick sinus syndrome. The lead was positioned within 2 to 20 minutes (average 5 minutes) after the selected vein was opened. Average acute peak to peak *P* wave amplitude was 5.17 mv (1.5 to 10 mv). Stimulation threshold at a 1 msec pulse width averaged 1.13 v (0.5 to 2.1 v). Three of the 53 electrodes became dislodged during up to 15 months of observation—1 during transfer from the catheterization laboratory to the patient's bed, 1 on the fifth postoperative day and 1 between the 4th and 12th postoperative weeks. Stable position of the lead could not be effected in the first of these cases. None of the 53 patients manifested exit block. The lead continues to perform well in 52 patients and results to date have been encouraging. Continued observation is necessary to verify that this lead offers long-term reliability.

Although atrial programmed cardiac stimulation offers the most physiologic form of treatment for the bradyarrhythmic heart, the implantation rate of pacemakers with this capability has been estimated to be only 1 percent worldwide.[1] The failure to utilize more fully and appreciate the potential benefits of atrial programmed stimulation is largely a result of past difficulties in securely positioning transvenous atrial electrodes of several designs for long-term pacing.[2] As a consequence, improvements in existing atrial pulse generators and the development of more sophisticated devices have generally been neglected. Recently, several atrial lead placement techniques that offer reliable performance have been presented.[2–15] As a result, our utilization of atrial systems has increased significantly.[16,17] In this report we present our experience in 53 patients with a new J type of atrial lead.

Material and Methods

From March 1972 to May 1976 we implanted pacemakers in 418 patients. Twenty-six percent of these patients (107 of 418) received atrial programmed devices. Between April 1975 and May 1976, atrial systems accounted for 46 percent (58 of 127) of pacemaker implantations in our practice. Atrial systems were provided for intermittent and permanent atrioventricular (A-V) block and for the sick sinus syndrome. Table I summarizes the types of atrial programmed pacemakers and their distribution in our study.

From March 1972 to April 1975 we relied on the transmediastinal retrocardial approach for implanting atrial electrodes.[11] We have since abandoned this approach, and the 58 subsequent patients receiving atrial systems have been given transvenously placed atrial leads. Five of the 58 received "hooking" type electrodes,[8] and the remaining 53 were given a new J type design.[18,19] This report is based on the latter 53 patients (32 women, 27 men, average age 66 years).

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TABLE I

Types of Pacemakers Used

Atrial Programmed Pacemaker System	Code*	Manufacturer	Model	Number	%
Inhibited	AAI	Biotronik	IDP-64	12	12
		Medtronic	5963	24	23
		CPI	...	1	1
Triggered	AAT	Biotronik	IRP-54	5	5
P-wave synchronous	VAT	Elema	EM156/50	6	6
		Biotronik	IVP-54	14	13
		Biotronik	IVP-64	37	36
		Biotronik	IKP-53	4	4
Sequential	DVI	...	...	...	...
Total				103	100

*Reference 20.

Lead configuration: The atrial lead reported (Medtronic model 6991) is similar in many respects to the Medtronic model 6907 ventricular lead. The atrial lead's distal portion is molded into a J shape, the short leg of the J containing three rows of three resilient silicone rubber tines offset from one another by an angle of 90°. (Fig. 1). The electrode is of platinum-iridium and has an active surface area of approximately 11 mm^2. A unique feature of the electrode is that it is canted inward toward the long connector portion of the lead. The rows of tines occupy the hemi-cylindrical portion of the short leg of the J most distant from the connector portion of the lead. The tines are provided to effect fixation within the atrium by becoming lodged in one or more interstitial spaces formed by the trabeculae within the appendage of the right atrium. In addition, the tines help coax the electrode tip into more intimate contact with the endocardial surface of the appendage (Fig. 2).

Placement of the lead: To facilitate passage through the external or internal jugular vein or a cephalic vein, the preformed J shape of the lead is straightened by means of a stylet. The lead is then pushed into the right atrium. Once in the atrium, the proximal portion of the lead is rotated so that the electrode portion points medially and forward toward the atrial appendage. Figure 3 shows that in the right appendage the lead lies ventromedially directly behind the sternum but is less close to the sternum than is the conus pulmonalis. The appendage itself varies in size among patients and can encompass relatively large portions of the atrium in some patients. If, with the electrode in the position described, the stylet is carefully withdrawn, the lead resumes its J shape and lodges itself in the trabecular network of this region.

Seating of the electrode is verified with continuous recording of the endoatrial signals and fluoroscopic observation of various breathing maneuvers and vigorous coughing (Fig. 4). Catapulting movements of the atrial electrode should not be evident during atrial systole. Additionally, the intraatrial action potential should be well defined and maintain its wave pattern over a series of cardiac cycles. Violent electrode motion or inconsistent action potential patterns, or both (Fig. 5), are indications of electrode flotation necessitating further efforts to achieve better position within the appendage. As a check against too much tension on the positioned electrode, a distinct J curvature should be evident during maximal inspiration.

After successful positioning of the electrode within the appendage, current and voltage thresholds were obtained at pulse widths of 0.25, 0.50 and 1.0 msec. Intraatrial electrograms were recorded oscillographically. Revision of the electrode position was attempted if thresholds appeared to be high or unstable or if atrial potentials were insufficient for reliable sensing pacemaker circuits.

The patients were ordered to 1 week of bed rest after implantation of the atrial pacemaker. During the first 2 weeks after implantation, standard electrocardiograms were recorded daily. In this manner a rough but sufficient basis for determination of sensing and capture behavior of the pacemaker system was available.

Results

The tined J lead was used to effect sensing or sensing and pacing in the 53 patients in whom it was implanted. Eighteen (34 percent) of the 53 patients received *P* wave

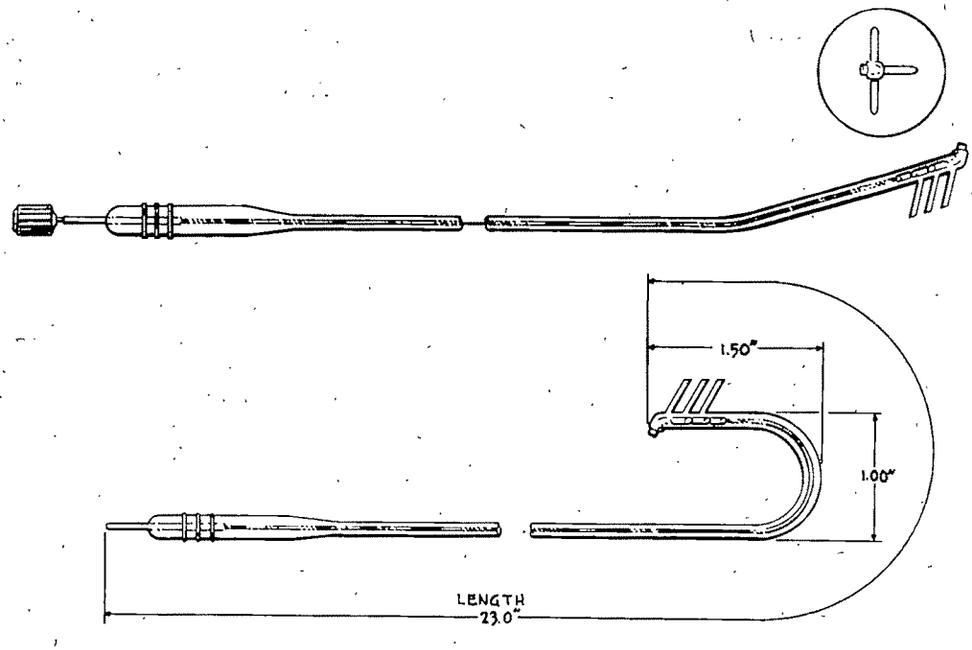


FIGURE 1. Schematic representation of the tined endocardial lead used in this study. **Bottom,** lead with stylet removed. **Top,** lead with guide stylet inserted. **Insert,** end view of distal portion of the lead showing tine arrangement.



FIGURE 2. Dissection of the right atrium and appendage of an 82 year old patient showing the tined J lead in position within the appendage. A transvenous ventricular lead is shown lateral to the J lead.

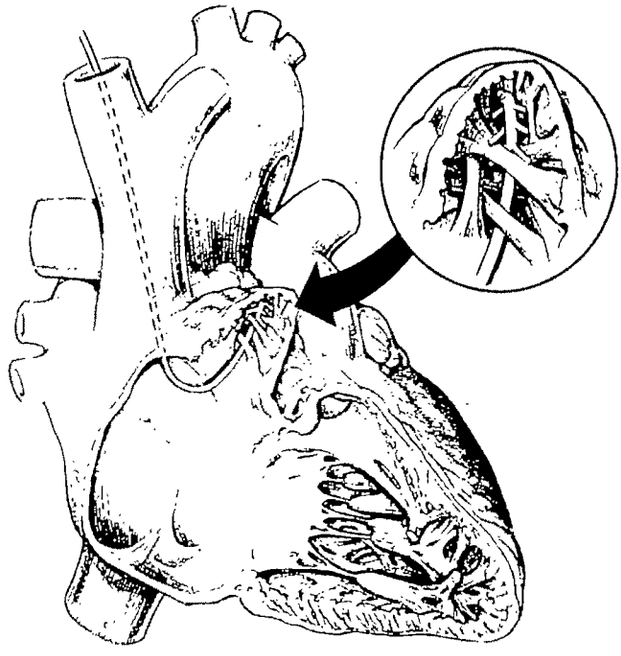


FIGURE 3. Diagrammatic representation of the lead in position in the right atrial appendage.



FIGURE 4. Lateral X-ray view of the lead in position in a 69 year old patient.

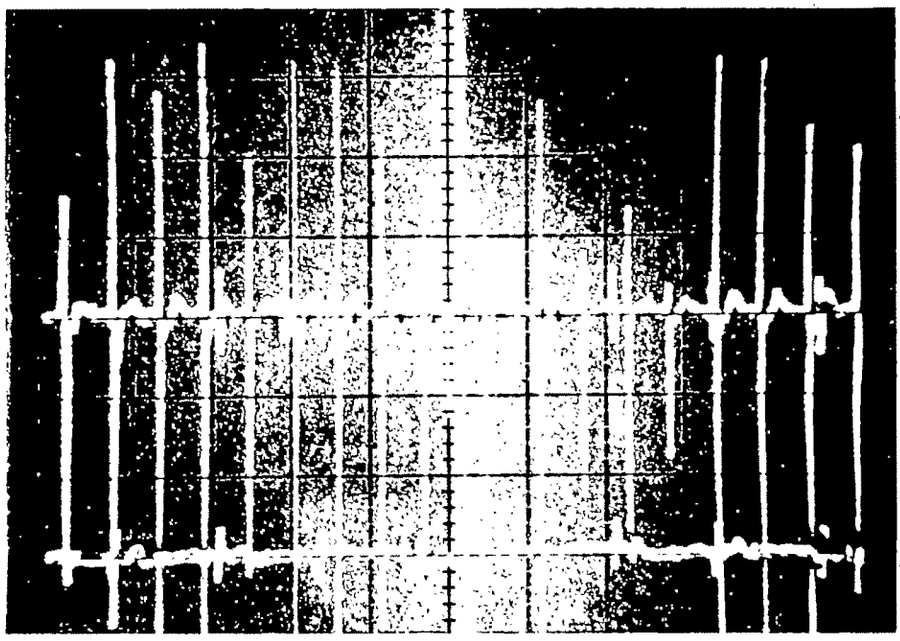


FIGURE 5. Electrogram obtained from a J lead positioned in the right atrial appendage. The varying amplitude of the wave form is an indication of electrode flotation. The lower tracing is a modified surface electrocardiogram for reference. Scale: 1 mv/vertical division; 1 sec/horizontal division.

synchronous devices (VAT) for the management of complete A-V block; 35 (66 percent) received atrial stimulating systems (AAT or AAI) (see Ref. 20) for management of the sick sinus syndrome.

The lead was introduced through the right external jugular vein in 29 patients (55 percent), through the right internal jugular vein in 21 (39 percent) and through the right cephalic vein in 3 (6 percent). Final positioning of the electrode was attained within 2 to 20 minutes (average 5 minutes) after the vein was opened. In one 66 year old patient, positioning of the electrode was difficult because an earlier left thoracotomy had produced a buckling of the central field, including a rotation and dorsal tipping of the heart. Consequently, location of the appendage could not be defined with certainty. In a 75 year old man with a pronounced sunken chest, the tined J lead could not be anchored in the appendage and the lead was withdrawn. This patient subsequently underwent cardiac pacing with a ventricular demand device (VVI) (see Ref. 20).

Atrial potential amplitudes: Table II lists the amplitudes of the atrial action potentials recorded from the tined J lead together with values previously obtained with other atrial leads. The J lead had a mean amplitude of 5.17 mv peak to peak (range 1.5 to 10 mv). In 60 percent of cases (32 of 53) the action potentials exceeded 5 mv; in only 5 cases were they less than 3 mv. Because the recorded amplitudes of the intraatrial electrogram were reasonably large, the pacemaker circuits were generally reliable in sensing the signal of this electrogram. One woman had amplitude-variable electrograms ranging from 1.5 to 4.0 mv without evidence of electrode flotation. Although it was questionable that her pacemaker's demand function was operating smoothly, this potential problem was of subordinate importance because the patient's sinus rate never exceeded 60/min during ergometric testing. In 10 cases (19 percent) a transient loss of sensing, and partial sensing during atrial flutter/fibrillation, was evident in the immediate postoperative period, unaccompanied by any clinically significant manifestations. In one woman, the lead was positioned too far within the atrium, causing flotation of the electrode within the appendage. By merely pulling back on the proximal portion of the lead, we were able to change the position of the lead and restore correct sensing operation.

TABLE II

Atrial Electrode Action Potentials in Three Lead Types

	Action Potential (mv)		
	EMT 588 (Elema) (no. = 37)	Hooking (Biotronik) (no. = 19)	Tined J Tip (Medtronic) (no. = 53)
Average	3.93	3.21	5.17
Maximum	10.00	7.00	10.00
Minimum	1.50	1.50	1.50

Dislodgments: In all, only 3 of the 53 electrodes became dislodged. One dislodgment occurred in a 64 year old patient who was the first to receive a tined J lead, undergoing implantation at a time when we lacked experience with this lead and with catheterization of the right appendage. The atrial lead dislodged into the fossa ovalis between the 4th and 12th postoperative weeks. Because the functional effectiveness of the lead was not demonstrably affected, we left it in this position for 12 months when, not unexpectedly, it suddenly stopped operating properly. The lead's position was then revised without difficulty.

The tined J tip lead was dislodged 5 days after initial implantation in the 66 year old patient with a prior thoracotomy

TABLE III

Stimulation Threshold in Three Lead Types

	Acute Threshold (volts)		
	EMT 588 (Elema) (no. = 7)	Hooking (Biotronik) (no. = 10)	Tined J Tip (Medtronic) (no. = 35)
0.25 msec pulse width			
Average	. . .	2.05	2.04
Maximum	. . .	4.00*	2.94
Minimum	. . .	1.00	1.05
0.50 msec pulse width			
Average	. . .	1.42	1.44
Maximum	. . .	3.30	2.53
Minimum	. . .	0.66	0.69
1.0 msec pulse width			
Average	2.31	1.04	1.13
Maximum	3.50	2.00	2.10
Minimum	1.70	0.47	0.58

*Threshold in one case was above 4.0 v and, therefore, was not measurable with our equipment.

cited earlier. As a result of buckling of the mediastinum, including cardiac rotation and tipping, we were not certain of the exact location of the electrode relative to the apex of the right appendage. Adequate visualization of the electrode at initial implantation was not possible because of a lack of capability for lateral fluoroscopy. This lead was repositioned successfully.

In the third case, a 64 year old patient, the lead was dislodged while the patient was being transferred from the X-ray table into bed. The lead was easily repositioned; however, the electrode appeared to be unstable on electrocardiography and fluoroscopy although the lead position itself was judged to be correct. We were unable to stabilize the electrode in this case and were compelled to implant a ventricular demand pacemaker (VVI).

Stimulation threshold (Table III): The threshold, recorded at a 1.0 msec pulse width for 35 cases (Fig. 6) receiving atrial stimulating pacemakers, averaged 1.13 v (maximum 2.1, minimum 0.58 v). These values were two to three times greater than initial thresholds we have observed in the right ventricle with similar surface area electrodes. This experience coincides with the experience of others.[21,22] In spite of the high initial values, we did not observe any cases of "exit block."

In all then, after a maximal observation period of 15 months, 52 of 53 tined J leads continue to operate without problems.

Discussion

Since 1972 our group has successfully implanted atrial programmed pacemakers in a significant portion of our patients. Our initial experience with the transmediastinal retrocardial approach produced a dislocation rate of approximately 14 percent. Larsson et al.[6] reported a dislocation rate of 9 to 10 percent which they found acceptable for those cases in which atrial programmed pacing was judged to be beneficial, but the attendant surgical requirements (that is, general anesthesia) rendered this technique suboptimal.

Results to date with the tined atrial J lead have been encouraging. For the first time we have available an

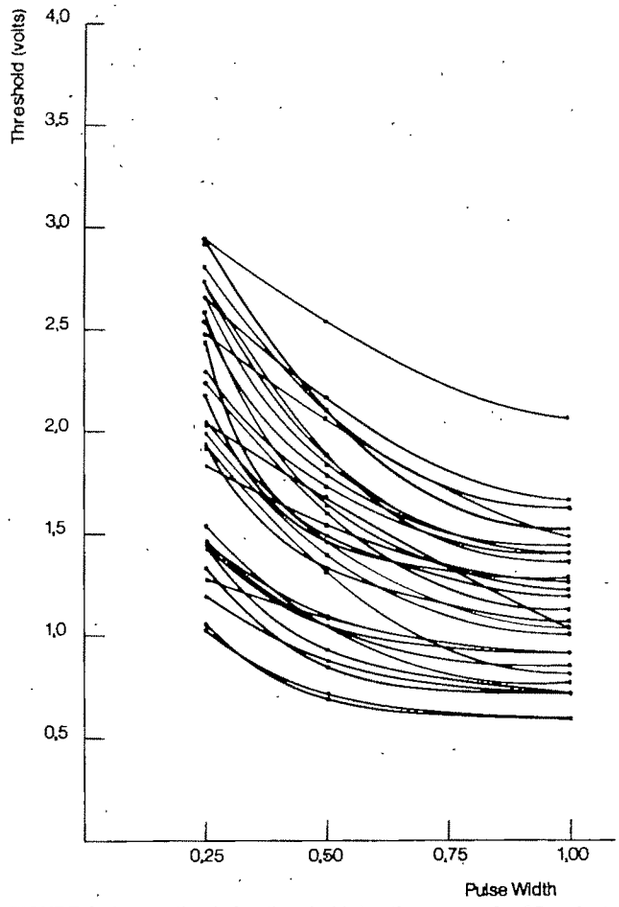


FIGURE 6. Acute stimulation threshold-duration curves for 35 patients at implantation, taken at a pulse width of 0.25, 0.50 and 1.00 msec.

atrial electrode that not only is easily and quickly implanted in the appendage of the right atrium but also has demonstrated very positive technobiologic properties. Most appealing has been the low dislodgment rate (6 percent; 3 of 53), which corresponds favorably with our experiences with "flanged" ventricular electrodes.

Advantages of new atrial lead: Several factors are responsible for the ease of positioning and long-term effectiveness of the lead. (1) Without doubt, the premolded J configuration of the lead is important for manipulating the electrode into the appendage and for providing a basic mechanism for maintaining electrode position. (2) The flexible silicone rubber tines serve a twofold purpose. Their main purpose is to become entangled with trabeculations within the appendage and thereby cooperate with the J shape to anchor the electrode. The arrangement of the tines also encourages the electrode itself to come into closer contact with the atrial endocardial surface. (3) Perhaps the key to the firm positioning and the unusually high peak to peak atrial potentials recorded is the off-center site of the electrode tip.

The relatively high atrial action potentials, which averaged 5.17 mv (minimum 1.5, maximum 10 mv), are noteworthy. To our knowledge, higher values with such

uniformity have not been reported. As a comparison, the atrial action potentials measured with the transmediastinal retrocardially placed leads averaged 3.9 mv (minimum 1.5, maximum 10 mv). The potentials measured with hooking electrodes had even lower values (Table II). Possible explanations for this behavior have been discussed previously.[17]

Potential problems: Initial atrial voltage thresholds (Table III) were two to three times higher than those obtained in the right ventricle with similar surface area electrodes. No significant deviations were found between the tined J lead and hooking atrial leads. These high initial thresholds have been cited as an argument against the implantation of atrial stimulating pacemakers. We have studied the threshold maturation characteristics of six hooking leads and have found them to have a much less pronounced threshold excursion than is common with ventricular leads. Thus, using standard commercially available pacemakers we have not observed exit block in any patient in whom we have implanted an atrial stimulator.

The increased effective lead diameter caused by the rubber tines at the distal portion of the lead dictated our selection and use of veins of large diameter to introduce the lead. We have found no clinical problems induced by the tines and have been able to reposition the electrode and completely remove the lead promptly and easily when indicated. No thromboses were observed in 10 patients who underwent angiographic studies 1 year after implantation. No perforation of the atrium has occurred.

Implications: Our results with the tined J lead strengthen the case for the increased application of atrial programmed pacemaker systems that we and others have recommended for hemodynamic reasons. The key to more widespread use of atrial systems may now be the availability of appropriate pacemakers and their reliable, interference-free operation. We believe that the tined atrial J lead meets all the requirements of a good lead. Continued evaluation and careful comparison of this lead with designs being studied by others are necessary.

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Exercise Testing in the Diagnosis of Coronary Heart Disease: A Perspective

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The methods of assessing the diagnostic usefulness of exercise testing in detecting coronary obstructive disease are examined. The limitations of long-term clinical follow-up and coronary angiography as standards for the determination of disease are described as are the effects of test methodology, criteria for positivity, prevalence of disease in the study population, reliability of the standard and recognition of false positive and false negative results in determining reliability of such testing.

High values were found for sensitivity and specificity for exercise testing of patients with coronary artery disease referred for consultation to medical center cardiology services. Maximal exercise testing and consideration of symptomatic and hemodynamic as well as electrocardiographic criteria for identification of myocardial ischemia are helpful in improving reliability. Diagnostic accuracy is greatly enhanced by recognition of known causes for false positive and false negative results.

Exercise testing detects coronary obstructive disease by eliciting objective evidence of myocardial ischemia in the form of transient upward or downward deviation of the S-T segment of the electrocardiogram when the cardiac work load is increased. In previous reports we[1–3] have discussed use of the exercise test in the diagnosis and prognosis of coronary heart disease.

A major challenge to the value of exercise stress testing for these purposes was presented in 1975 in a report by Borer et al.,[4] who stated that the "diagnostic usefulness of exercise electrocardiography is limited. False negative responses are frequent in patients with clinically suspected coronary disease and false positive responses are frequent in asymptomatic patients." Although their report was immediately criticized in several published letters to the editor,[5,6] we believe that its conclusions require careful scrutiny so that the role of exercise testing in the diagnostic study of coronary heart disease might be better defined. This presentation is intended to (1) examine some of the problems inherent in determining whether exercise testing is useful as a diagnostic test for coronary heart disease, (2) define situations in which such testing may be helpful and those in which it will not be and (3) compare exercise tests with other tests used in the diagnosis of coronary heart disease.

Problems in Assessing Usefulness for Diagnosis

Most studies attempting to assess the usefulness (that is, sensitivity and specificity) of exercise testing in diagnosing coronary obstructive disease have relied on the behavior of the S-T segment alone as the index of a positive or negative ischemic response. Definitions of sensitivity and specificity and predictive value are derived from the Latin square tabulation (Fig. 1). How "useful" exercise testing is depends on the accuracy with which it detects existing and predicts future coronary heart disease.

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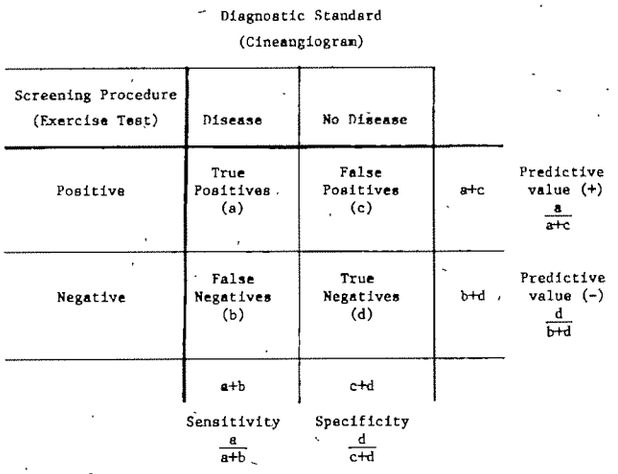


FIGURE 1. Latin square diagram from which are derived definitions of sensitivity, specificity and predictive value of positive and negative exercise tests. The diagnostic standard for determining the presence or absence of coronary obstructive disease is the coronary cineangiogram, and the criterion for positivity of the test is deviation of the S-T segment of the electrocardiogram, either upward or downward.

Standard for Comparison

To determine the accuracy of a method of assessing the presence or absence of a disease one must have an accurate, preferably infallible, *standard* of diagnosis with which to compare any diagnostic test. Two standards are used today to assess the presence or severity of coronary heart disease in the living subject: (1) long-term clinical follow-up to assess the presence or absence of significant coronary events such as angina, myocardial infarction or coronary death; and (2) coronary cineangiography.

Clinical follow-up: How accurate are the standards? Long-term clinical follow-up is a noninvasive standard, but it requires years of waiting for the appearance of the clinical manifestations defining the true incidence of coronary disease. In a follow-up study[7] of the prognostic value of the double Master two-step test, 15 years were required before the sensitivity and specificity of the test could be significantly evaluated. Even then one could not be certain that a negative test was a false negative test if the patient later manifested coronary disease: There had been ample time for the development of new obstructive disease in the years after performance of the test.

Coronary angiography: Another standard for defining the presence or absence of disease is the coronary angiogram. In a study of the reliability of interpretation of the coronary angiogram,[8] intraobserver agreement (agreement with oneself on a subsequent reading) ranged from 63 to 92 percent. When individual readers were evaluated, the more experienced readers (who had read more than 700 angiograms) demonstrated more intraobserver consistency and greater agreement with the consensus than did less experienced readers. The standard deviation of reader to reader variability in assessing percent stenosis in angiograms has been estimated to be 21 percent.[9] Intra- and interobserver variability in reading the angiogram must thus be a factor contributing to the discrepancies encountered in correlating the exercise test with angiographic findings.

The amount of coronary arterial narrowing required to produce myocardial ischemia during exercise is disputed. Borer et al.[4] used 50 percent narrowing in the major part of their study as the indicator of obstructive disease. Recent studies[10,11] indicate that even at maximal hyperemic flow rates there is almost no impairment of coronary blood flow with arterial obstruction of 50 percent. Seventy-five percent obstruction reduces maximal hyperemic flow only 33 percent. Inability to increase coronary flow occurs when coronary constriction reaches 88 to 90 percent of arterial diameter. Thus an ischemic response to exercise testing cannot be expected until coronary arterial narrowing exceeds 75 percent.

The precise relation between percent stenosis determined from angiographic measurements of vessel diameter and anatomic stenosis as percent compromise of the lumen observed in pathologic studies has not been defined. It has been shown[12] that the degree of stenosis tends to be consistently underestimated in angiographic compared with pathologic studies.

The sensitivity rate of an exercise test will necessarily be low if the test is expected to detect 50 percent obstruction of a coronary vessel because this degree of narrowing is not likely to cause myocardial ischemia. There will be a greater concurrence of exercise test and angiographic findings if 75 percent rather than 50 percent obstruction is taken as the goal for detection. Thus, neither clinical follow-up nor coronary angiograms approach the ideal diagnostic standard of infallibility.

The Adequate Exercise Stress Test

Testing to maximum: Exercise tests must be performed in a way that yields as much information as possible. According to Cumming,[13] a submaximal test carried to 85 percent of the predicted maximal heart rate may miss 50 percent of the ischemic responses that could be found by carrying the test to maximal effort. For maximal diagnostic sensitivity, whether the standard is long-term follow-up or coronary angiography, exercise testing must be carried to physiologic or symptom-limited maximal effort. A physiologic maximum is reached when there is objective evidence of all-out effort, that is, no change or a decrease in blood pressure, heart rate or oxygen consumption with increasing work loads. At symptom-limited maximal effort the patient is fully aware of distressful discomfort recognized as angina pectoris, inappropriate breathlessness or leg claudication severe enough to stop him. We have found it helpful to grade symptoms from 1+ to 4+, 1+ indicating mild but definite, 2+ moderate, 3+ moderately severe and 4+ maximally severe symptoms. For an adequate test the patient should be encouraged to exercise at least to the 1+ level to ensure that the symptomatic end point is a significant one.

The development of significant arrhythmia or limiting noncardiac symptoms (for example, quadriceps

fatigue on the bicycle ergometer) may preclude attainment of maximal effort levels. In such instances test results are inconclusive and should not be considered falsely negative if they do not demonstrate ischemic responses in patients with angiographically documented obstructive disease.

Familiarity with the test procedure: Patients should be familiar with the exercise testing procedure, either from prior testing or from an initial practice run performed at least 1 hour before the test. Familiarity augments reproducibility.[14] When assessing the usefulness of exercise testing it may be inappropriate to compare angiographic findings with the results of the first exercise test ever performed by a patient.

Steady state measurements: Diagnostic exercise testing patterns should allow patients enough time at each stage to achieve a steady state. Barnard et al.[15] found that two thirds of a group of firemen who had normal responses on previous maximal treadmill tests showed an ischemic electrocardiographic response to sudden high intensity treadmill exercise that did not permit them to attain a steady state. These apparent false positive results were attributed to hemodynamically generated subendocardial ischemia due to lack of prior warm-up. These were false positive results in the sense that the S-T depression did not identify coronary obstruction, but they were true positive tests in the sense that they indicated ischemia, probably subendocardial ischemia of hemodynamic origin.

Dealing with False Positive and False Negative Results

False positive tests: Known causes of false positive and false negative tests must be eliminated if one wishes to make a fair assessment of S-T segment deviation alone as an indicator of coronary arterial obstruction. One must eliminate the effects of other variables including the effects of digitalis, diuretic agents (probably through potassium depletion) and some sedatives and antidepressant drugs known to yield exercise S-T depression that disappears after drug withdrawal.[16] Valvular heart disease, mitral click-murmur syndrome,[17] left or right ventricular hypertrophy[18] and congestive cardiomyopathy are known to give rise to S-T depression in the exercise electrocardiogram, probably through hemodynamic deprivation of subendocardial perfusion. Wolff-Parkinson-White syndrome and left bundle branch block may produce S-T depression during exercise presumably because of the abnormal sequence of repolarization. Patients with hyperdynamic states such as vasoregulatory asthenia,[19] those with early hypertension who have an inordinately large increase in blood pressure during exercise, some persons with asymmetric septal hypertrophy, persons whose T waves invert during hyperventiliation[20] and also young women with the so-called syndrome X all may exhibit S-T depression during exercise in the absence of coronary arterial narrowing. It is possible that all of these states may represent an excessive response to normal catecholamine production or normal response to excess catecholamine production.

False negative tests: Known causes of false negative tests include administration of nitroglycerin-like drugs and propranolol, which are particularly likely to obscure the ischemic electrocardiographic response in submaximal testing. Right bundle branch block and prior myocardial infarctions may so distort the repolarization pathways that S-T depression does not emerge. Failure to accept as positive some forms of J point depression with slow upsloping of the S-T segment also accounts for some false negative tests. Stuart and Ellestad[21] point out that an upsloping S-T segment that remains more than 2 mm below the baseline 0.08 second beyond the S wave has as much prognostic significance for coronary events as horizontal depression of the same magnitude. Downsloping of the depressed S-T segment was shown to have a stronger prognostic significance for coronary events than either upsloping or horizontal depression. Thus, the upsloping but depressed S-T segment is often a true positive indicator hitherto interpreted as negative.

Another category of false negative results is found among patients who have fully recovered from myocardial infarction and display no ischemic manifestations on exercise testing. The results must be classified as false negative because the patients have documented coronary disease, most having at least one completely occluded coronary artery. Yet, after the healing of the scar of the infarct, the remaining viable myocardium may be adequately perfused by wide open coronary arteries producing no evidence of ischemia. The negative exercise test in these patients is in fact a true negative result because it identifies a nonischemic response, but by the rigors of definition and criteria it must be classified as a false negative finding.

Angina or decreasing blood pressure during testing: Detection of the ischemic response to testing requires more than inspection of the exercise electrocardiogram for the presence of S-T segment depression or elevation during and after exercise. If S-T deviation is accompanied by typical anginal distress, a true positive result is extremely likely. However, if typical angina is generated during a test in which S-T segment deviation cannot be discerned, the test might also be interpreted as showing a true positive result, particularly if the angina proves reversible with administration of nitroglycerin during continued uninterrupted exercise. In our experience, progressively decreasing systolic blood pressure during increasing work loads is also a strong indicator of myocardial ischemia even in the absence of pain or characteristic electrocardiographic changes, provided that valvular heart disease, prior myocardial infarction or cardiomyopathy accounting for decreased pumping capacity of the heart has been ruled out. Either typical anginal pain with convincing relief with nitroglycerin during uninterrupted exercise or decreasing blood pressure as described may be the clue to significant coronary disease when healed myocardial infarction, right bundle branch block, left bundle branch block or Wolff-Parkinson-White syndrome preclude interpretation based on ST-T deviation.

The ischemic response to exercise testing thus has at least three components—electrical (electrocardio-

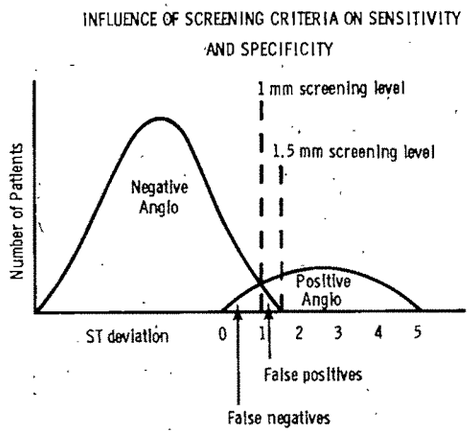


FIGURE 2. Diagram showing how changing the criterion for test positivity from 1 mm of S-T segment depression to 1.5 mm will eliminate all false positive results but will increase the number of false negative results. Anglo = coronary angiogram.

graphic), hemodynamic (blood pressure) and symptomatic (angina). Clinical interpretation of an exercise test is greatly enhanced by taking into account all three components. If the electrocardiographic response happens to be obscured or rendered uninterpretable it may become possible to detect the ischemic state by one or two of the other manifestations.

Proper screening criteria: The screening criteria used to define positivity also influence the usefulness of exercise testing. As with coronary angiography, sensitivity and specificity may be varied by changing the level at which the test is considered positive. A change in the level that increases the sensitivity will decrease the specificity and vice versa. For example (Fig. 2), if the degree of S-T depression required for an "ischemic" response is increased from 1 to 1.5 mm, the specificity of the test increases from 89 to 100 percent whereas its sensitivity decreases from 62 to 48 percent[22]; that is, if one requires more S-T depression for a positive test, coronary disease will be absent in all patients with a negative result test, but more false negative tests will fail to identify patients with disease who would have been recognized on the basis of the less stringent criteria.

Consistency in interpretation of the exercise electrocardiogram: When all the requirements for an adequate exercise test have been met, discrepancies may remain due to intra- and interobserver variation in interpreting the exercise electrocardiogram. When 38 exercise electrocardiograms were given to 14 cardiologists, Blackburn's survey group[23] reported a 10-fold difference in the frequency of "abnormal" readings among observers. Disagreement was greater on exercise than on postexercise records. Observers were more likely to agree with their own blind interpretation made on another occasion than with other observers.

Comparisons between exercise test results and angiographic results are thus significantly influenced by inconsistencies in interpretation of both the exercise test and the coronary angiogram. A system of duplicate readings by two observers (of either the exercise test or the angiogram) followed by adjudication of their differences has been found to be a highly repeatable method and should be used to minimize the effect of variation in interpretation.[24] Previous studies of correlations (or lack of correlations) between the exercise test and the angiogram have not employed this system.

Epidemiologic Concepts

Definitive diagnosis for all: Even if one compared accurately performed and interpreted exercise tests with accurately performed and interpreted angiograms and used appropriate screening criteria for both, other factors would influence the agreement between the exercise and angiographic findings: (1) availability of a diagnosis definitively established for *all* screened patients; (2) prevalence of the disease in the population studied; and (3) changes in the predictive value of a test used in conjunction with other tests.

The moral limitations of human research impose restrictions on methods available to determine the usefulness of exercise stress testing, evaluated against the standard of cineangiographic determination of coronary obstruction. In studies such as that reported by Borer et al.,[4] it is usually considered not justifiable to subject persons with nonischemic exercise test responses to angiography. Yet Thorner and Remein[25] point out that "the evaluation of sensitivity and specificity requires that a diagnosis for the disease under study be established or ruled out for every person tested regardless of whether the person screened negative or positive." If all negative tests were falsely negative, the sensitivity of the exercise tests would be even lower than the 30 percent value reported by Borer et al.[4] for patients with known coronary disease. However, if all those with negative exercise tests had negative angiograms, there would be no false negative responses, hence sensitivity would be 100 percent!* One cannot evaluate the sensitivity of the exercise test in a group of asymptomatic subjects unless angiograms are obtained in all. "No disease" must be confirmed by a method independent of the exercise test.

Influence of prevalence: The prevalence of a disease in the population studied also influences the diagnostic usefulness of a test (Table I). The predictive value of a positive test increases with increasing prevalence of the disease in the study population. When 2 percent of a population is known to have a disease then the presence of the disease can be predicted by a test in only 27.9 percent of the population. However, when the prevalence rate is 50 percent, the disease can be correctly diagnosed with a test in 95 percent of cases. If the prevalence rate were 75 percent, the disease would be correctly predicted in 98.3 percent of cases.[26]

The predictive value of the exercise test for coronary disease is very high only if one studies a population with

* Sensitivity = $\frac{\text{true positives}}{\text{true positives} + \text{false negatives}}$

TABLE I

Relation of Prevalence of a Disease and Predictive Value of a Test*†

Actual Disease Prevalence (%)	Predictive Value of a Positive Test (%)	Predictive Value of a Negative Test (%)
1	16.1	99.9
2	27.9	99.9
5	50.0	99.7
10	67.9	99.4
20	82.6	98.7
50	95.0	95.0
75	98.3	83.7
100	100.0	—

* From Vecchio TH: Predictive value of a single diagnostic test in unselected populations. *N Engl J Med* 274:1171–1173, 1966.
† Sensitivity and specificity rates each equal 95 percent.

a known large prevalence of the disease, such as patients referred to a medical center for evaluation of chest pain. Conversely, when screening young asymptomatic adults without risk factors who are physically active and asymptomatic, the yield of positive tests, and presumably of angiograms demonstrating coronary obstruction is very small and there are numerous false positive results.[27] Among middle-aged patients with chest pain and risk factors, the yield of positive responses concurrent with angiographic documentation of obstructive disease is 96 percent (at Montefiore Hospital).

Sequential screening: The predictive value of a particular test is also related to whether that test is used alone or in conjunction with other tests. For example, using data from the Framingham study with clinical follow-up, Epstein[28] found that the predictive value of the cholesterol level more than doubled when it was combined with various other risk factors (Table II). In a study by Mandel et al.[29] normal coronary angiograms could be predicted in all of a small population sample who had fewer than three major coronary risk factors, normal physical examination, normal chest roentgenogram and electrocardiogram and negative exercise test.

For Which Patients Is Exercise Testing Useful?

To provide an illustration of the use of exercise testing in the setting of a cardiology consulting service in a major hospital center (University of California at Los Angeles) and to assess the sensitivity and specificity of the test under such circumstances, one of us (AAK) analyzed the last 205 exercise tests that he had conducted (Table III). The majority of tests were performed in order to diagnose ischemic heart disease, and 75 of the 205 patients underwent coronary angiography. Forty-three tests were performed as follow-up studies to evaluate therapeutic progress and to assess the natural history of coronary disease; 27 tests were performed primarily to test physical fitness or to assess the severity of impairment imposed by known disease. The analysis of sensitivity and specificity of these tests (Fig. 3) in-

TABLE II

Predictive Value of a Combination of Tests

Risk Factor	Predictive Value of a Positive Test x	Predictive Value of a Negative Test Δ	Risk Ratio x/Δ
Cholesterol >260 mg/100 ml	21	10	2.1
Cholesterol >260 mg/100 ml and BP >160/95 mm Hg	27	11	2.5
Cholesterol >260 mg/100 ml and BP >160/95 mm Hg and LVH	35	10	3.5
Cholesterol >260 mg/100 ml and BP >160/95 mm Hg and smoking >10 cigs/day and weight >1.15 X observed-desirable	44	9	4.9

x % of cohort with positive test who will develop manifestations of coronary disease within ten years.
Δ % of cohort with negative test who will develop manifestations of coronary disease within 10 years.
BP = blood pressure; cigs = cigarettes; LVH = left ventricular hypertrophy.

TABLE III

205 Successive Treadmill Tests

	no.	%
Ischemic heart disease study		
With coronary angiograms	75	41
Without angiograms	60	34
Follow-up tests	43	24
Total	178	100
Functional capacity and special studies	27	13

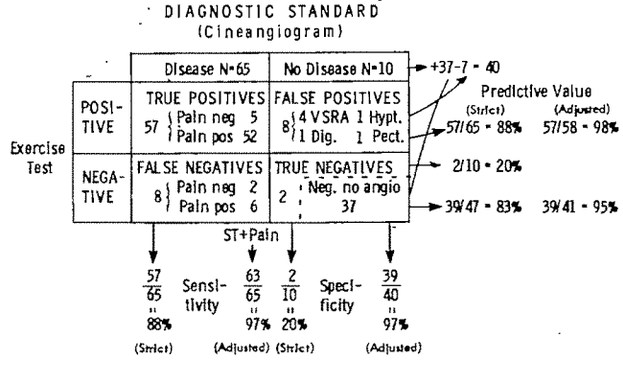


FIGURE 3. Latin square diagram illustrating recent experience with exercise testing of 75 patients who had coronary angiograms and 37 patients with negative tests and no angiograms. Rates for sensitivity, specificity and predictive value can vary widely depending on the criteria set for positivity of the test and the strictness of the diagnostic standard. Dig. = digitalis effect; Hypt. = hypertension; N = number of patients; neg = negative; Pect. = pectus excavatum; pos = positive; VSRA = vasoregulatory asthenia.

dicated that of the 65 subjects with angiographically proved obstructive disease, 57 had true positive tests by strict criteria, yielding a sensitivity rate of 88 percent. Of the eight with false negative tests, six had classic anginal pain generated by the exercise. If these are considered true positive tests, the sensitivity rate rises to 97 percent.

Among the patients with no disease who had positive exercise tests by strict criteria, seven had clearly recognizable false positive results; four of these had vasoregulatory asthenia*, one had digitalis effect, one had a severe hypertensive response to the exercise and one had pectus excavatum. With only two true negative and eight false positive results, the specificity rate is poor, 20 percent by strict criteria. However, if one eliminates the seven false positive results recognized as such and adds in as true negative results the pain-free, negative tests of 37 patients who had no angiograms, then the number of subjects classified as having no disease becomes 40 and the specificity rate of testing becomes 97 percent. Furthermore, when so adjusted, the predictive value of a positive test becomes 98 percent instead of 88 percent by strict criteria and the predictive value of a negative test becomes 95 percent rather than 83 percent by strict criteria.

These data suggest that many false positive and false negative tests are not truly false and that among patients in a large cardiology consulting service in whom the prevalent rate of coronary disease is high, both the sensitivity and the specificity levels of the exercise test are high.

In screening middle-aged sedentary subjects, in whom one may assume that approximately 10 percent of the group has asymptomatic coronary disease, the predictive value of a negative test yields a 99.4 percent probability that the angiogram is free of evidence of obstructive disease.[26]

In screening persons with a high cholesterol level, as in the study of Borer et al.,[4] the sensitivity rate of the cholesterol measurement in predicting coronary heart disease in persons 40 to 59 years old is about 27 percent and the specificity rate about 86 percent.[28] The 12 percent prevalence rate of coronary disease in a study population acquired by lipid screening will yield predictably low sensitivity and specificity rates for the exercise test. The usefulness of exercise testing in this group could be enhanced by making the electrocardiographic screening criteria more strict (for example, using 2 mm S-T depression rather than 1 mm), using maximal rather than submaximal tests and using the exercise test in conjunction with other predictors of coronary disease such as blood pressure, smoking habit and the occurrence of chest pain. The intended use of the results of testing determines to some extent the strictness of the criteria for positivity. If all positive responders are to be subjected to coronary angiography with its small inherent risk, it is desirable to minimize false positive results by using the stricter criteria for positivity of 2 rather than 1 mm S-T depression. If the plan calls for long-term clinical follow-up and additional factors are taken into account such as presence of pain, blood pressure response and risk factors, one might use more liberal criteria for positivity because subjects with false positive tests would not be exposed to additional risk.

Occasionally there may be good reason to do an exercise test for diagnostic purposes even in persons with known coronary heart disease. For example, after a myocardial infarction, ischemia may be demonstrated in the noninfarcted areas of the heart, thereby identifying a high risk condition. The mechanism of puzzling symptoms may be elucidated—exercise-precipitated arrhythmia, papillary muscle dysfunction or inadequate blood pressure response implying poor left ventricular function.

TABLE IV

Sensitivity and Specificity of Various Diagnostic Methods for Coronary Heart Disease Compared with Angiography

Test	Sensitivity (%)	Specificity (%)	Reference
Clinical judgment	88–91	76	Kelemen et al.[30]
Holter monitoring	91	78	Stern et al.[31]
Master 2 step	84	73	Cohn et al.[32]
Atrial pacing	73	40	Kelemen et al.[30]
Hypoxemia	72	33	Kassebaum et al.[34]
Resting ECG	50	69	Cohn et al.[32]

ECG = electrocardiogram.

Comparison With Other Diagnostic Tests for Coronary Disease

For exercise testing to be used widely in the diagnosis of coronary heart disease, it must offer advantages over other current techniques available for the same purpose. Table IV lists some of these techniques and their respective sensitivity and specificity rates. Each is compared with angiographic findings as the standard.

These values must be viewed with reservations for the following reasons: (1) In the evaluation of clinical judgment as a diagnostic method,[30] subjects with a negative history did not have angiograms; the lack of a confirmed diagnosis in all subjects thus creates a bias in the results. (2) In the Holter monitoring study,[31] isolated T wave changes were considered positive in the exercise test, and angiographic evidence of coronary obstruction of less than 70 percent was considered significant. If the data are recalculated excluding isolated T wave changes as ischemic, and accepting only obstruction of 70 percent or greater of vessel diameter on angiography as significant, the sensitivity and specificity values become 68 and 78 percent, respectively.

Comparison of the Master two-step test and angiography by Cohn et al.[32] yielded higher correlations than the study of Jelinek et al.,[33] which reported 61

* Postural T wave inversion, excessively fast heart rate for the exercise performed and complete reversal of electrocardiographic changes with 20 mg of orally administered propranolol.

percent sensitivity rate. The improved sensitivity in the Cohn study may have resulted from considering Master tests that did not cause an increase in heart rate to over 110 beats as uninterpretable.

The atrial pacing test,[30] reported to be 73 percent sensitive and 40 percent specific, does result in 60 percent false positive and 27 percent false negative responses, yielding a low predictive value. It is the only invasive test on the list.

The hypoxemia test data for sensitivity and specificity[34] were derived from comparison with coronary angiograms some of which show only 50 percent obstruction of a vessel; comparisons made between hypoxemia and exercise testing in that study include the interpretation of J point depression as a positive exercise test, a criterion not deemed valid by the majority of exercise testers.

The resting electrocardiographic data in the study of Cohn et al.[32] are lower than the figures of Stern et al.,[31] who reported a 61 percent sensitivity rate for the resting tracing in detecting coronary heart disease.

Myocardial imaging with intravenously injected potassium-43[35] *or thallium-201*[36] has been reported[35] to have high sensitivity and specificity when carried out immediately after maximal exercise testing demonstrating an ischemic electrocardiographic response. Additional cases will have to be studied to verify these early data.

Implications: At this time no test is distinctly superior to exercise testing in predicting or ruling out coronary artery disease. Extensive debate on the relative usefulness of the various tests and correlations with coronary angiography or long-term follow-up will thus not resolve this issue. Furthermore, attempts to assess the usefulness of exercise testing on the basis of sensitivity, specificity and predictive value appear to be unreliable and the results often predetermined. The conclusions based on the data can be made to vary corresponding to the bias of the analyzer and depend on the selection of screening criteria, test population, comparative standard and method of testing (differences in end point, reproducibility, inter- and intraobserver variability).

We suggest that the concepts of sensitivity and specificity of exercise testing are based on the false premise that such physiologic testing can be expected to identify anatomic arterial obstruction. The test actually identifies a myocardial ischemic response. When such a response is elicited, coronary obstructive disease can be inferred only when other possible causes for myocardial ischemia have been eliminated by clinical study.

Conclusions

The clinician treating patients with suspected heart disease is confronted with conflicting views on the value of exercise testing as a *diagnostic* method for detecting coronary obstructive disease. There is little dispute regarding the value of such testing in assessing the severity of functional impairment or the effectiveness of therapeutic interventions such as drug administration, exercise training or surgical revascularization and in following up the natural history of coronary artery disease.

Doubts about diagnostic value have been kindled by the study of Borer et al.[4] in which it was assumed that a submaximal exercise test would be adequate to detect an ischemic response in subjects with coronary arterial obstructions of 50 percent or less of the vessel diameter using 1 mm of horizontal or downsloping S-T segment depression in the exercise electrocardiogram as the criterion for positivity. Poor sensitivity and specificity were found when the study population consisted of a variety of subjects whose common characteristic was hyperlipidemia. The difficulties and inaccuracies inherent in using these procedures and methods have been described earlier.

We believe that exercise testing has great value in the diagnosis of coronary obstructive disease when it is used as a clinical tool in conjunction with the information obtained from the history, physical examination, resting electrocardiogram and basic laboratory analyses. When clinical study raises suspicion of the presence of coronary obstructive disease, a properly done exercise test can support the diagnosis with objective evidence when it is present, and negate it when it is not. It is necessary that all manifestations of the ischemic exercise response (electrocardiographic, symptomatic and hemodynamic) be sought for and taken into consideration in the interpretation.

Exercise testing as a mass screening measure can be used appropriately as a technique for detecting coronary disease provided that the population tested is expected to have a substantial rather than an insignificant prevalence of coronary disease. It should be used in conjunction with other screening techniques and carried to maximal effort, and the criteria for positivity should be varied in accord with the expected yield. Within the limits of these guidelines, exercise testing may be expected to serve as a useful and dependable aid in the diagnosis of obstructive coronary heart disease.

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Primary Prevention of Coronary Heart Disease: A Critique

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The question is whether alteration of risk factors will aid primary and secondary prevention of coronary heart disease. Critical review of available evidence indicates that inferences have been made about the beneficial effects of risk factor modification without an adequate test of the hypothesis. Trial interventions to assess the efficacy of serum cholesterol-lowering measures have had negative or equivocal results. It remains to be seen whether the findings of clinical trials on hypertension can be applied toward primary prevention of coronary heart disease in the community. The cigarette smoking habit seems to be unique among coronary heart disease risk factors. The evidence appears sufficient to justify serious consideration of a strategy of preventing the smoking habit now, persuading patients to stop and encouraging teenagers not to start.

Our present knowledge of coronary heart disease is derived from the accumulated results of more than 200 years of clinicopathologic observations,[1,2] laboratory experiments[3–5] and epidemiologic investigations.[6–8] Yet, despite advances in medical science and technology, the epidemic of atherosclerosis and its clinical manifestations in the form of occlusive diseases of the arteries and sudden death continue unabated.[8,9] This is so despite indications that mortality from coronary heart disease in the United States has decreased since 1968,[10] perhaps in part because of heroic efforts to reduce hospital and prehospital deaths.

Obviously we still need a greater reduction in mortality than any hitherto achieved by the sophistication of modern cardiology before a major impact on coronary heart disease will be felt in the community as a whole. We can no longer rely entirely on our "hit or miss" strategy of treating the sick. To do so would mean continuing to battle "in the wrong place and far too late in the day." [11] The history of medicine demonstrates that the medical profession (despite its achievements) has never been able to control an epidemic by merely treating the sick. The present day epidemic of coronary heart disease is no exception. Even if we could afford the luxury, we have neither the manpower nor the resources necessary for attempting such a course.

Is Primary Prevention Feasible?

The question is whether *primary prevention* of coronary heart disease is now feasible.[12–15] Lest today's controversies surrounding single or multiple risk factor intervention for primary prevention of coronary heart disease cause us "... to wander too far from the Palace of Truth ...,"[16] we must scrutinize objectively our understanding of the pathogenesis of coronary heart disease and hence our capability for primary prevention. Can we reverse or alter the disease process by modifying coronary heart disease risk factors? Is risk-factor modification effective or even safe? Have we rigorously tested the lipid hypothesis? Do we have enough evidence to warrant risk factor modification in our daily practice

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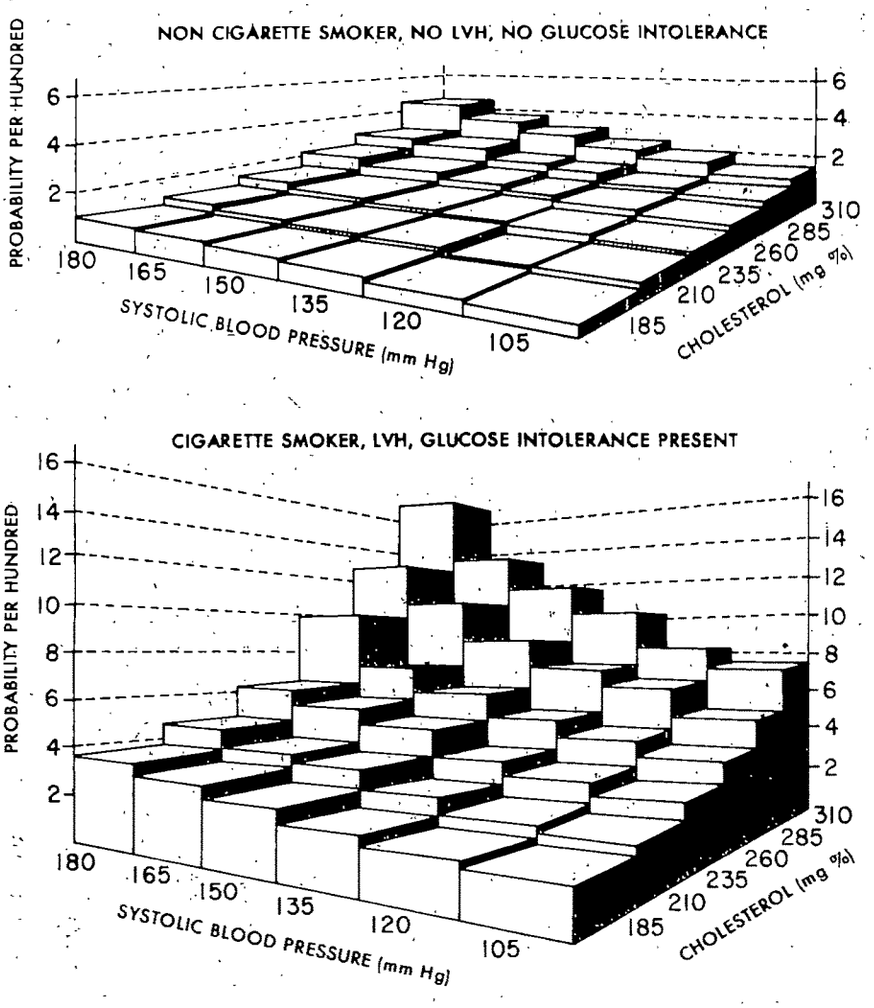


FIGURE 1. Probability that a 35 year old man will have coronary heart disease in 6 years as related to systolic blood pressure, serum cholesterol, left ventricular hypertrophy (LVH) by electrocardiogram, cigarette smoking and glucose intolerance.

of medicine, as a means of primary prevention of coronary heart disease? Do we have enough evidence to recommend changes in people's life style when our recommendation implies a drastic socioeconomic and political change, with significant psychologic overtones?

Two points of view prevail with respect to these questions. Some investigators advocate the development of a "strategy for primary prevention," based on the inference derived from the available data.[8] Others believe that the case for establishing a strategy for primary prevention of coronary heart disease at this time, especially with regard to the management of hyperlipidemia, is based only on a *premise* that "... has not yet been proved true to the satisfaction of epidemiologists and biostatisticians, or the medical community at large ...."[15]

The main thrust of this paper, therefore, is to examine the available evidence on the efficacy of risk factor modification on prevention of coronary heart disease. If the results published to date from the various intervention trials are not sufficient to warrant mass community prevention programs then, as suggested by Ahrens,[15] we must consider "... a step-wise approach to more appropriately planned tests of the hypothesis, leading eventually to preventive measures starting in childhood."

Of the risk factors related to coronary heart disease, three stand out, especially in combination with other factors, in light of all epidemiologic findings.[17] These are the level of serum cholesterol, systolic and diastolic blood pressure and the habit of cigarette smoking. In considering the implications of these three risk factors for primary prevention of coronary heart disease, emphasis should be placed on the interaction of these factors with each other and with other factors. As shown by the data in Figure 1 (given only as an example to illustrate the point), the probability (per 100) is 0.5 that a 35 year old white man will have coronary heart disease in 6 years if his systolic blood pressure is 135 mm Hg and serum cholesterol is 185 mg/dl and if he does not smoke cigarettes and has no major physical abnormalities (such as glucose intolerance or evidence of left ventricular hypertrophy). An independent change in any of these factors is associated with a slight or modest change in the probability of coronary heart disease. Yet the probability, relative to the basic rate in the very lowest risk group, increases dramatically when two or

three of these factors are present in combination with other clinical abnormalities. For example, the probability that our 35 year old man will have coronary heart disease in 6 years increases to 16.9 (per 100) when, in addition to hypercholesterolemia, hypertension and cigarette smoking, he exhibits electrocardiographic evidence of left ventricular hypertrophy and has abnormal glucose tolerance (lower panel, Fig. 1).

The Lipid Hypothesis

The lipid hypothesis, based on available epidemiologic data relating the level of serum cholesterol to the incidence of coronary heart disease, maintains that reducing the level of serum cholesterol will lead to a reduction in the incidence of coronary heart disease. This hypothesis has been tested in both secondary and primary prevention trials.

Secondary Prevention Trials

Foremost among secondary prevention trials are those conducted in Great Britain,[18–21] Norway[22] and the United States.[23–27] The results obtained in these trials confirm what had been demonstrated convincingly in the past, namely, that plasma lipid levels can be intentionally altered. However, the data were either negative or at best equivocal in demonstrating the potential benefits of plasma lipid-lowering measures in prevention of morbid events or mortality, or both. Some of the factors leading to the equivocal results of these trials have been reviewed adequately by Ahrens[15] and I will not discuss them in detail here. However, a brief description of each trial and its findings is relevant.

Studies conducted in Great Britain: In one of the earliest intervention trials, Rose et al.[18] studied the effect of vegetable oil and restricted saturated fats in the diet of patients with a history of previous myocardial infarction. A total of 80 patients were assigned randomly to three treatment groups (corn oil, olive oil and control group) and were followed up for about 2 years. Although the level of serum cholesterol was reduced in the group treated with vegetable oil, the proportion of patients remaining alive at the end of the study was higher in the control than in the treated groups. The investigators concluded that vegetable oil "... cannot be recommended as a treatment of ischemic heart disease. It is most unlikely to be beneficial, and it is possibly harmful."[18]

In another study,[19] conducted and reported by a research committee of the British Medical Research Council, 393 men who had recovered from a first attack of myocardial infarction were randomly allocated to an experimental diet (low in saturated fats and containing 85 g of soybean oil) or to a regular diet. The follow-up lasted 2 to 7 years. The investigators observed an immediate and highly significant reduction (22 percent) in the level of serum cholesterol among the test diet group, but no difference in mortality between the two groups. At the end of the study the number of major recurrences of myocardial infarction and deaths due to coronary heart disease were "identical in the two groups." [19]

In two other studies[20,21] clofibrate was used as a means of reducing serum cholesterol. In one of these,[20] patients with a previously documented history of angina pectoris or acute myocardial infarction, or both, were randomly assigned to a regimen of either clofibrate or placebo and followed up for 6 years. Although by the end of the study serum cholesterol was reduced in the group treated with clofibrate, there was no difference between the two study groups in mortality and frequency of nonfatal recurrent myocardial infarction. Only among patients with a history of angina pectoris was there a reduction in mortality in the clofibrate-treated group. The results of the other study,[21] conducted in the region of Newcastle upon Tyne, indicated a sustained reduction in the level of serum cholesterol throughout the 5 years of the study, and decreased mortality and reduced recurrence of myocardial infarction in the clofibrate-treated group than in the control subjects. However, the "protective" action of the drug against myocardial infarction and death bore no relation to its cholesterol-reducing effect.

The Norwegian study: The secondary prevention trial in Norway[22] was designed to test the efficacy of diet in recurrent myocardial infarction and mortality; 412 men, aged 30 to 64 years, with previously documented myocardial infarction were separated into two groups of 206 each. One group was prescribed a diet low in saturated fats and cholesterol and high in polyunsaturated fats (experimental diet); the other group received a regular Norwegian diet (control group). The groups were followed up for 5 years. The level of serum cholesterol was significantly reduced among patients on the experimental diet and the reduction was maintained throughout the study. However, there was no difference between the two groups in the incidence of sudden death and mortality from cardiovascular disease.

The U. S. study: The U. S. Coronary Drug Project[23–27] is perhaps the most extensive secondary prevention trial in coronary heart disease conducted thus far. Its design and methodology have made it one of the best controlled studies in the field of clinical trials. Its main objective was to "... test the efficacy and safety of several lipid-lipoprotein-influencing drugs in the long-term therapy of coronary heart disease in men aged 30 to 64 years with proven previous myocardial infarction ...." [23] A total of 8,341 patients were randomly allocated to six different groups: conjugated estrogens 2.5 mg/day, conjugated estrogens 5.0 mg/day, clofibrate 1.8 g/day, dextrothyroxine-sodium 6.0 mg/day, niacin 3.0 g/day and placebo. The first allocation to treatment was in 1966 and the last in 1969. By 1970 the regimen of 5.0 mg of estrogen was discontinued because of an "excess number of nonfatal cardiovascular events in this group compared to placebo." [24] In 1971 the dextrothyroxine regimen was discontinued for the same reason.[25] Estrogens in a dose of 2.5 mg/day were discontinued in 1973 because there was no evidence of any beneficial effect and some suggestion of "harmful trends." [26] Finally, in 1975 the Coronary Drug Project Research Group reported its findings on clofibrate and niacin.[27] The results indicated a significant reduction in the levels of serum cholesterol and triglyceride in both the clofibrate- and the niacin-treated groups. Although smaller than had been anticipated in the design of the study, the reduction was "... achieved and maintained throughout the follow-up period." [27] However, the drug-treated and placebo-treated groups did not differ in cardiovascular disease mortality or death from all causes (death occurred in 25.5 percent of those given clofibrate and in 25.4 percent of those given placebo.)[27] For the combination of events (death due to coronary heart disease or definite nonfatal myocardial infarction), the incidence rate was 23.8 percent for the clofibrate-treated group and 26.2 percent for the placebo-treated group. This small difference was not statistically significant.[27] Results in the niacin-treated group were similar. Five-year death rates due to coronary heart disease were "nearly identical" for the group given niacin and that given placebo. On the basis of these findings, the Coronary Drug Project Research Group concluded that "...

there is no evidence of significant efficacy of clofibrate with regard to total mortality and cause-specific mortality . . . ." [27] The conclusion was similar for niacin.

Primary Prevention Trials

Although the question of the feasibility of dietary intervention to test the lipid hypothesis was answered in the affirmative by results of the National Diet-Heart Study in 1968,[28] the National Heart, Lung, and Blood Institute decided not to enlarge this feasibility study into a national dietary intervention trial in the United States. Available evidence on the potential benefits from reducing serum cholesterol for primary prevention of coronary heart disease is therefore limited to the results of the studies conducted among special population subgroups in New York,[29] Helsinki,[30] Chicago[31] and Los Angeles.[32]

Two additional intervention trails designed to test the lipid hypothesis should be added to this list. One is a dietary test of the hypothesis conducted by Frantz et al.[33]; the other is The World Health Organization Cooperative Trial of clofibrate.[34] The latter is still in progress, and the results are not yet available. The former, published as an abstract, reported too few deaths among subjects in the trial to provide adequate information for discussion. A brief review of the methods and results of the others will follow.

The New York study: This study is known as the New York Anti-Coronary Club study. The investigators entered 1,242 volunteer men aged 40 to 59 years into the study. Of these, 941 were judged free of prior evidence of coronary heart disease and given an experimental diet (called prudent diet) composed of 18 percent protein, 42 percent carbohydrate and 40 percent fat (60 percent of the total fat in the diet was derived from mono- and polyunsaturated fats). The polyunsaturated/saturated fat ratio of the diet was estimated at 1.25 to 1.50. The original objective was to determine whether the experimental diet was acceptable to the subjects and could reduce the level of serum cholesterol. Thus, during the original 2 year period no control subjects were selected. Later 457 control subjects aged 40 to 59 years were chosen from among men who had voluntarily appeared in a cancer detection clinic and were judged free of coronary heart disease by the same criteria applied to the experimental group. Although the experimental group and control subjects were judged by the investigators to be "quite comparable" in levels of serum cholesterol, the experimental group had "higher proportions of men with initial obesity and hypertension" than did the control group.[29] Further, by the end of the study, 532 of the original 941 men in the experimental group had "lapsed into an inactive status"; and, for serum cholesterol determination, only 104 of the original men in the experimental group were followed up for more than 7 years.

Serum cholesterol was reduced in the 104 men in the experimental group from 253.1 to 228.4 mg/dl. Conversely, the 197 men in the control group had an average reduction from 251.9 to 245.5 mg/dl, a difference of 18.3 mg/dl between the two groups. The reported incidence of "new coronary events" per 1,000 person-years of observation among the active experimental, inactive experimental and control groups was, respectively, 4.3, 7.4 and 10.2.[29]

The Anti-Coronary Club study of New York demonstrated that the cholesterol-reducing diet is acceptable to a free-living (albeit volunteer) population even though some have questioned the nutritional adequacy of such a "prudent" diet. The study further showed that the level of serum cholesterol could be lowered by a regimen of "prudent" diet and counseling. However, the study's findings cannot (and should not) be interpreted as indicative of the efficacy of a "prudent" diet for primary prevention of coronary heart disease. The study did not provide an adequate and acceptable test of the lipid hypothesis. Its participants were chosen from among volunteers who "responded to a radio and press call"; furthermore, they were not randomly assigned to experimental and control diet groups. Thus, one cannot be confident that the subjects were comparable from any point of view except diet. Even the question of acceptability and feasibility of a cholesterol-reducing (prudent) diet was, for all practical purposes, settled more convincingly by results of the National Diet-Heart Feasibility Study.[28] The real question is the efficacy of such a cholesterol-lowering diet in primary (or secondary) prevention of coronary heart disease. The results of the New York study do not justify an affirmative answer to this question. Inadequate study design (lack of both randomization and double-blind procedures), less than satisfactory adherence record among participants, selectivity of participants (that is, use of volunteers) and, perhaps most important, after the fact analysis of the data impose serious restrictions upon the applicability of the results to primary prevention of coronary heart disease in the community.

The Helsinki study: This study[30] of the effectiveness of a cholesterol-lowering diet on mortality from coronary heart disease was initiated in Finland in 1958 among patients in two mental hospitals (referred to as hospital N and hospital K). During phase I (1959 to 1965), patients in hospital N were fed a low cholesterol diet whereas patients in hospital K (who served as "control" subjects) received a regular diet. The diets of the two hospitals were reversed in phase II of the study (1966 to 1971). The study lasted 12 years. Among the men, the age-adjusted mortality rate from coronary heart disease (per 1,000 person-years of observation) during 1959 to 1965 was 5.7 in hospital N (diet) and 15.2 in hospital K (control subjects). Corresponding rates for the period 1966 to 1971 were 7.5 in hospital K (diet) and 12.9 in hospital N (control subjects).

For women, the age-adjusted mortality rate (per 1,000 person-years) from coronary heart disease during phase I of the study was 3.9 in hospital N (diet) and 8.1 in hospital K (control subjects). During phase II, the rates were 7.7 in hospital N (control subjects) and 6.5 in hospital K (diet). The pattern for general mortality (death from all causes) was similar to that for coronary heart disease; that is, in each hospital the death rate was higher when the patients were on the control diet than when they were on the experimental diet. The only exception was in women in hospital K, who had a higher rate of death from all causes (total mortality) when on the experimental diet than when on the control diet (30.7 versus 25.8). Pooled data from both hospitals for both phases I and II indicated a pattern consistent with the findings in each hospital at the end of each phase of the study. For men, the age-adjusted mortality rate from coronary heart disease per 1,000 person-years was 6.6 among those on the diet and 14.1 in control subjects; for women the corresponding rates were 5.2 and 7.9.

Unfortunately, these findings do not provide an adequate test of the lipid hypothesis. There were serious shortcomings in the study design and the analysis of the data.[13,15,35] In hospital K the rate of death from all causes among female patients actually increased from 25.8 to 30.7 (per 1,000 person-years) when the diet was changed to the cholesterol-reducing diet although death rates from coronary heart disease

in the same group decreased slightly (from 8.1 to 6.5). Certainly the situation in hospital K was quite different from that of hospital N (at least among the female patients). The authors recognize the problem but attribute the difference to "... shorter stays and higher turn-over ..." of patients during phase II of the study. In other words, many of the long-term patients were removed during phase I. However, this situation should result in a lower death rate in phase II, not the higher rate as reported. Further, as others[13] have noted, the explanation itself poses another serious methodologic problem in the design of the study: This study was not really a crossover trial. In a typical crossover trial, different schedules (in this case cholesterol-reducing diet and regular diet) are "... successively administered to an unchanging pool of patients, and on each patient the response variable is measured twice." [13] This was not the procedure followed in the Helsinki study. Further, the patients (in hospitals N and K) were not randomized to receive one of the two schedules (that is, cholesterol-reducing diet and regular diet) in a crossover fashion. The results, therefore, cannot be interpreted as being due to changes in the diet between the two hospitals during the two phases of the study. The observed differences in mortality from coronary heart disease "... may be due to different policies of medical care (e.g., length of stay), of selection of patients (e.g., change in rate of intake of high-risk patients), etc...." [35]

Perhaps the selection bias is the most serious problem in interpreting the results of this study, especially since the main end point was death[13]: "... mortality is a response variable which can be ascertained only once on each patient so that those available for study in the second period are a selected group of survivors of those studied in the first period ...."

The Chicago study: Enlisted in this study,[31] initiated in 1958, were 519 volunteer men aged 40 to 59 years recruited from several industrial firms in Chicago. The men were judged to be free of coronary heart disease at entry into the study. The purpose of this study was to test the hypothesis that mortality would be reduced by controlling five major risk factors (hypercholesterolemia, hypertension, obesity, cigarette smoking and physical inactivity), but the investigators carried out a systematic and sustained process of education to increase motivation to control the intake of saturated fats, cholesterol and total calories. Thus, "... modification of nutritional habits ..." became "... the primary and major effort of the program ...." [31] Therefore, this study has been considered a primary prevention trial aimed at testing the lipid hypothesis even though the design and method of analysis do not justify this conclusion. For example, the participants were not randomized into experimental and control groups. Evaluation of the efficacy of the intervention program was based on a comparison between the nondropouts and dropouts, on one hand, and a comparison between the mortality experience in the group under observation and the estimated mortality rates for men of similar age and at equivalent risk of coronary heart disease as reported by epidemiologic studies in the United States (for example, U. S. Pooling Project). Overall data on mortality (death from all causes, death due to coronary heart disease and sudden death) indicate "... a trend in favor of the intervention program participants compared with the Pooling Project men." [31]

It should be recognized that the lipid hypothesis is based on the relation documented between the level of serum cholesterol and the incidence of coronary heart disease in prospective studies of the general population (for example, the Framingham study). A comparison between the mortality experience of a group of volunteers who choose to participate in an intervention trial and the incidence of the same end point estimated from the general population studies cannot be considered a valid test of the hypothesis. The investigators recognized these limitations and drew only "tentative" conclusions from their findings. Nevertheless, the findings should not be interpreted as evidence in favor of the lipid hypothesis.

The Los Angeles study: This trial was initiated among the domiciliary population of the Los Angeles Veterans Administration Hospital in 1959.[32] Of 1,095 men who volunteered to participate, 846 were chosen and were assigned randomly into experimental (424 men) and control (422 men) dietary regimens. All the men chosen were judged free of coronary heart disease at entry; all were 55 years old or more. The experimental diet was a diet low in saturated fats and cholesterol, and *high* in polyunsaturated fats. The control group received a regular hospital diet. The primary end point of the study was coronary heart disease, manifested either as sudden death or an acute myocardial infarction. By the end of the study, the number of such "hard" end points was significantly greater in the control group than among those consuming the experimental diet (119 versus 85).

Two important observations in the Los Angeles study need emphasis. First, cigarette smoking differed significantly ($P < 0.01$) between the experimental and control groups. The proportion of cigarette smokers was higher among the control subjects than in those consuming the experimental diet, as was the proportion of heavy smokers (17 versus 3 percent). To what extent the difference in smoking between the two groups accounts for the difference in mortality (and nonfatal myocardial infarction) is not known. Because cigarette smoking exerts a great and independent influence upon the incidence of myocardial infarction and sudden death, the observed difference in smoking habits between the two groups should not be dismissed lightly, especially since there were more men in the control group than the experimental group whose smoking habit was not ascertained (58 versus 41). Second, and perhaps more important, is the observation that during the 8 years of follow-up there were 31 deaths due to cancer in the experimental diet group, compared with 17 in the control group ($P = 0.06$).[36] Excess death due to cancer among the experimental group contributed to the fact that at the end of the study there was no difference in total mortality (death from all causes) between the two groups. The investigators of the Los Angeles study, recognizing the limitations of their findings, concluded "... we consider our own trial, with or without the support of other published data, to have fallen short of providing a definitive and final answer concerning dietary prevention of heart disease." [32]

Current Status of the Lipid Hypothesis

It is clear that both secondary and primary prevention trials conducted to test the validity of the lipid hypothesis—that is, the efficacy of serum cholesterol-lowering measures (dietary or otherwise) on mortality or morbidity—have yielded either negative or inconclusive results. As pointed out by Ahrens,[15] these results "... lead us to no clear-cut conclusion that the effort was worth the cost ...."

Among the secondary prevention trials, perhaps the most revealing is the U. S. Coronary Drug Project. In terms of methodology (both in design and analysis) the study could be considered a classic trial; one can hardly find a flaw. The study was a well controlled clinical trial in which all participating centers presumably adhered to the provisions of a standardized (and centrally con-

trolled and monitored) protocol. All data were collected uniformly under the supervision of a capable coordinating center. Analysis of the data was *not* after the fact. Rather, the research was meticulously conducted, testing specific hypotheses articulated in advance. The study's negative findings are therefore significant. They indicate, without need for additional data, that serum cholesterol-reducing measures are not likely to be effective in *secondary prevention* of coronary heart disease. This conclusion should not come as a surprise in light of our knowledge of lipid metabolism, frequency distribution of different types of hyperlipidemia in the general population and shortcomings inherent in secondary prevention trials.

Primary prevention trials aimed at testing the lipid hypothesis are in a situation similar to that of secondary prevention trials. Further, most of these studies (unlike the U. S. Coronary Drug Project) suffer from methodologic shortcomings, including inadequate study design and analysis, inadequate numbers, inadequate (and sometimes total lack of) randomization and lack of double-blinding; most statistical procedures used in these studies are of doubtful applicability to the extent that "... no results of intervention studies to date are as statistically significant as their P-value calculations indicate...." [14]

Perhaps the most intriguing question surrounding the current status of the lipid hypothesis is the difference in the frequency distribution of different types of hyperlipidemia in the general population and among different age groups. For example, it is well known that men "... with one or another monogenic form of hyperlipidemia ... are the very men whose plasma lipids are least responsive to dietary or drug manipulation ...." [15] In addition, recently it has been reported that "significantly higher low density lipoprotein cholesterol and total triglyceride are present in whites (with high incidence of coronary heart disease); while higher high density lipoprotein cholesterol is found in blacks (with low incidence of coronary heart disease), in age, sex, total serum cholesterol matched comparisons...." [37] It appears that the high density lipoprotein cholesterol could have a very special function, that is, to exert an inhibitory effect on atherogenesis.

In summary, it appears that "... despite a very considerable scientific effort and some tantalizingly suggestive results, we have no clear-cut, generally accepted answer to the question of whether cholesterol-lowering measures can affect coronary heart disease ...." [14] Obviously, we have not adequately tested the lipid hypothesis. We do not know whether reduction in the level of serum cholesterol will decrease the incidence of coronary heart disease. If we had the answer there would be no need for elaborate and costly experimental epidemiologic studies such as the Multiple Risk Factor Intervention Trial Programs,[38,39] and the Lipid Research Clinics.[40] As we await the outcome of these experimental epidemiologic studies, it is important to heed Ahren's advice that "... efforts now be made by clinical researchers to gain a better understanding of the differences in pathogenic defects leading to hyperlipidemia, so as to tailor most appropriately the diet/drug manipulation to those individuals sharing the same kind of defect...." [15]

Arterial Blood Pressure and Prevention of Coronary Heart Disease

The prospects have risen sharply in recent years that primary prevention of major complications of atherosclerosis may be achieved through control of hypertension. The main reason for optimism has been clinical trials indicating efficacy of treatment of hypertension.[41,42] Results of these clinical trials have demonstrated the clinical effectiveness of treatment to reduce blood pressure on the incidence of major complications of atherosclerosis, especially stroke. However, the demonstrated efficacy of treatment has been less conclusive with regard to coronary heart disease. Further, the evidence on the effectiveness of antihypertensive therapy is limited to the results of clinical trials among *selected* hypertensive persons with sustained elevation of blood pressure, while the risk of coronary heart disease has been demonstrated to be related to *casual* blood pressure readings in the general population. It is not known whether the efficacy of antihypertensive therapy can be replicated in community programs for the purpose of primary prevention of coronary heart disease. Community clinical trials of hypertension currently underway in the United States, for example, the Hypertension Detection and Follow-Up Program,[43] are of great importance in providing the final answer to the question of whether mass community-based hypertension detection and treatment can accomplish the task of primary prevention of coronary heart disease and reduce mortality and morbidity associated with it.

Cigarette Smoking and Prevention of Coronary Heart Disease

Cigarette smoking is unique among all risk factors in coronary heart disease. Unlike serum cholesterol and blood pressure, where doubt remains about the potential efficacy of their alteration, the scientific conditions prerequisite to launching a massive public health program against cigarette smoking have been met. It has been demonstrated that the cigarette smoking habit increases the risk of coronary heart disease, that the habit can be altered and that abandoning the habit will reduce the risk even though there has been no formal double-blind controlled clinical trial.[6–8,17,31,44–51]

The available evidence indicates that total mortality (death from all causes) is about twice as high among cigarette smokers as among nonsmokers. Of this excess mortality, 19 percent is due to excess death in lung cancer but 37 percent is due to excess mortality from coronary heart disease.[51] Cigarette smoking enhances significantly the effect of other coronary heart disease risk factors (Fig. 1). At any given level of risk, the habit of cigarette smoking almost doubles that risk. Obviously, cigarette smoking is more dangerous among those who are already at high risk than among those who are at lower risk (Fig. 1). The influence of cigarette smoking in accelerating the effect of other risk factors (such as hypertension) on the incidence of coronary

heart disease is so great that it must receive a high priority for alteration.

Stamler[31] summarizing the Chicago Coronary Prevention Evaluation Study stated, "... these data strongly suggest that continued cigarette smoking is associated with very high risk of premature death for coronary prone men and that other preventive measures are by themselves of limited value ... as long as they fail to give up cigarette smoking ...." [31]

Foremost among the available evidence in favor of potential benefits in stopping the habit of cigarette smoking are results from the following studies.

Study of mortality among British physicians: The study of the effect of cigarette smoking on mortality among British physicians was a prospective study, with death as its end point.[45,46] At the end of a 10 year follow-up period, the death rate per 1,000 was 0.03 in nonsmokers, 0.05 in former smokers and 0.23 in heavy smokers. Among the 865 persons who died solely as a result of acute myocardial infarction, the death rate per 1,000 was 2.12 in nonsmokers, 2.76 in former smokers and 3.79 in heavy smokers. In both situations the death rate among former smokers was almost identical to that of nonsmokers.

The Dorn study of smoking and mortality among U. S. veterans: The cohort of the Dorn study, initiated by him in 1954, comprised 293,658 U. S. veterans.[44] This prospective study yielded 2,265,674 person-years of observation by 1962. A total of 46,270 deaths had occurred among the cohort during the 8 1/2 years of follow-up. Risk of death was associated with the numbers of cigarettes smoked, duration of the smoking habit and intensity of inhalation. The most impressive finding was the downward trend in risk of death among former smokers; as the duration of time from stopping the habit increased, there was a corresponding decrease in death rate. The findings show a clear pattern of regular and steady decrease in risk of dying with increasing time from discontinuance of smoking.

Study of 1 million men and women: This prospective study, initiated in 1959 and 1960 and continued for 6 years, enrolled more than 1 million men and women over age 30 years.[47,48] The mortality experience, at the end of the follow-up period, was related to the cohort's smoking history at entry into the study. Among men of all age groups and in women under 70 years, the death rate from coronary heart disease was higher among smokers than among nonsmokers. Death rates among former smokers decreased as the period of discontinuance lengthened.

Thus, the case against cigarette smoking is epidemiologically as convincing as one could expect. The findings of the studies cited gain added significance when one considers the totally independent influence of cigarette smoking on the risk of coronary heart disease.[52] There is a consistency about the evidence on the relation between cigarette smoking and the incidence of coronary heart disease that makes smoking perhaps the most important of all coronary heart disease risk factors in terms of prevention. The U. S. Surgeon-General[50] and the Royal College of Physicians of London[49] concluded that cigarette smoking is a danger to cardiovascular health and that stopping the habit can be an effective measure for primary prevention of cardiovascular disease. We concur in view of the results of clinical, epidemiologic and laboratory studies conducted in the United States and elsewhere (for example, the findings of studies among migrants),[53,54] the recent observations in countries such as Italy that have had a low death rate from coronary heart disease but are now experiencing a steep increase in death rate corresponding to a sudden and dramatic rise in per capita cigarette consumption[55] and the results of studies cited earlier. They all indicate a potential dramatic reduction in mortality with a reduction in the number of persons who smoke cigarettes.

> "... from the viewpoint of both causation and care, the most significant finding ... is the experience of those who have stopped smoking ... the coronary heart disease death rate among ex-smokers falls steadily ... until after ten years of abstinence the survivors experience death rates close to those of non-smokers." [51]

Behavioral and psychologic factors among smokers: Surely, one must always consider the crucial question of whether the smoker or the smoking is the culprit. There is a strong suggestion that a person's behavioral and psychologic characteristics make him prone to coronary heart disease and that the nature of these characteristics dictates the habit of cigarette smoking. In other words, those who smoke are, for genetic or constitutional reasons, quite different persons from nonsmokers and are susceptible to coronary heart disease. We should therefore focus on why a person smokes cigarettes rather than on the cigarette itself. As plausible as these explanations may seem, recent epidemiologic data, especially the observed changes in male to female mortality ratio from coronary heart disease (corresponding with an alarming increase in the cigarette smoking habit among girls and women) make that proposition seem quite unlikely[51,55]:

> "... that genetic or constitutional factors play a part in the natural history of ischemic heart disease cannot be denied; and some of the differences between the mortality experience in smokers and non-smokers may well be explained by coincidental differences in temperament or physique. Nevertheless, there is enough unanimity in the evidence from epidemiological, clinical, and laboratory research to allow the conclusion that cigarette smoking certainly aggravates the manifestations of ischemic heart disease, ... (and) giving up smoking over a long period is associated with a lowering in the risk of death from ischemic heart disease ...."

Conclusions

It is clear that coronary heart disease remains the leading national health problem. Results of clinicopathologic, laboratory and epidemiologic investigations of the past 200 years have provided us with a wealth of knowledge on the natural history of this disease, but the etiologic mechanism continues to elude us, emphasizing the need for new horizons in research.

Cholesterol-lowering measures: The association between the level of serum cholesterol and the incidence of coronary heart disease forms the basis for the *lipid hypothesis* that cholesterol-lowering measures (dietary or otherwise) will lead to a reduction in the incidence of this disease. Unfortunately, the lipid hypothesis has not been tested adequately to the satisfaction of the medical community. All primary and secondary intervention trials conducted thus far have reported negative

or equivocal results. Further, most of these trials suffer from inadequate numbers, lack of randomization or other serious methodologic shortcomings. The U. S. Coronary Drug Project is perhaps the only secondary prevention trial that is exempt from this criticism; but it provided totally negative results. Among primary prevention trials, perhaps the WHO Cooperative Trial could, when completed, shed some light on the controversy of the lipid hypothesis. There are serious doubts that this will be the case. As pointed out by Ahrens, "It is a reasonable guess that sequential analysis of deaths from new coronary heart disease events . . . failed to show a significantly lower rate in the test group than that in the placebo group; if that result *had* been obtained, I suspect that the investigators would have felt bound to terminate the trial and declare that the drug had been proved to be beneficial." [15]

Multiple risk factor interventions: A constellation of factors, mostly environmental but some genetic, are associated with the incidence of coronary heart disease. Among all such factors, three stand out, for when they are present in combination with other factors (for example, diabetes and evidence of left ventricular hypertrophy) the risk of coronary heart disease increases many fold. These are levels of serum cholesterol, systolic and diastolic blood pressure and the habit of cigarette smoking. The Multiple Risk Factor Intervention Trial (MRFIT) and similar experimental epidemiologic investigations (for example, LRC) should be encouraged to complete their task to determine if we can prevent mortality and morbidity associated with coronary heart disease by modification of these risk factors as a means of primary prevention. In addition, if these trials fail to provide positive results we must be prepared for ". . . a plan for a new major research thrust against our nation's most destructive disease process . . . ." [56] There is no doubt that we must concentrate our efforts on increased basic research into the mechanism of atherosclerosis and the formation of plaques in the arterial wall, pleading for and justifying increased support for this area of research.

Control of hypertension: With regard to hypertension, the final answer to the question of whether early detection and proper treatment of mild and moderate elevation of arterial blood pressure (that is, diastolic blood pressure of 90 to 104 mm Hg) will prevent subsequent mortality and morbidity from coronary heart disease must await the results of the clinical community trials (for example HDFP). In the meantime, practicing cardiologists and all physicians should consider the concept of the control of hypertension in light of the basic principles of the epidemiology of blood pressure. That is, arterial blood pressure is a biologic quantity, with a continuous distribution. The adverse effects of hypertension are numerically related to the level of blood pressure; there is no dividing line (or cutoff point) above which an individual patient is at risk of coronary heart disease and below which he is free from it. Physicians should "individualize" each treatment plan to the needs of the patient and keep the patient's motivation high so that he will adhere to his therapeutic regimen.

Cessation of cigarette smoking: Finally, as we await the outcome of the experimental epidemiologic studies on the efficacy of risk factor modification and as we continue our efforts to gain a better understanding of the pathogenic mechanism of coronary heart disease and the process of atherosclerosis, we can perform an invaluable service toward preventing coronary heart disease by strongly advising our patients (especially those with multiple risk factors) to stop smoking now. Although most cigarette smokers are aware that the habit carries danger, they slight the relevance of this knowledge to themselves, delay quitting and are not informed about the strength of the evidence. Physicians therefore (especially cardiologists) have a unique opportunity in practicing preventive medicine by educating their patients, convincing them that the effects of cigarette smoking are real and relevant to them and dangerous to their health and helping them to quit the habit. Until we learn more about the role of the lipid hypothesis and control of hypertension in prevention of coronary heart disease, one of the most rewarding activities in today's medical practice could be advice on smoking, because if even a relatively small reduction in the death rate from coronary heart disease were to result a great number of lives would be saved. Because it is much easier not to start smoking than to stop, our clinical efforts toward prevention of coronary heart disease should be directed primarily toward the pediatric age group, especially since it takes a few years for the beneficial effects to appear. Although it is never too late to quit smoking, it is much better not to start the habit at all. Our task therefore becomes one of convincing teenagers, especially girls who have picked up the habit to a much more accelerated rate than boys, not to start smoking.

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PROGRESS REPORT

Collaborative US-USSR Study on the Prevalence of Dyslipoproteinemias and Ischemic Heart Disease in American and Soviet Populations*

Prepared by the US-USSR Steering Committee for Problem Area 1: the Pathogenesis of Atherosclerosis†

The ongoing collaborative US-USSR study of the prevalence of dyslipoproteinemias, based on the Lipid Research Clinics Study protocol, is described. The purpose of this multidisciplinary, multiclinic program is to investigate the relation of plasma lipids and lipoproteins and other risk factors to atherosclerotic disease in selected populations. The research design, sampling strategy and general hypotheses of the study are detailed. Common quality control methods and standardized screening procedures used in data collection are reviewed. Components of the study include measurement of plasma lipids and lipoproteins, the collection of demographic and physiologic information, a 24-hour dietary recall, administration of the Rose questionnaire and resting and exercise electrocardiograms. Preliminary comparative data for total plasma cholesterol, triglycerides and high density lipoprotein cholesterol are presented for men aged 40 to 59 years.

The US-USSR Joint Program in Cardiovascular Diseases has received considerable emphasis both in the United States and in the Union of Soviet Socialist Republics. Heart disease is the principal cause of death in both countries and was judged an appropriate subject for joint international study after individual proposals advanced by scientific experts were evaluated and areas of cooperation were identified.

The collaborative US-USSR Lipid Research Clinics Study is one component in the large set of activities. The following summary is an overview of the US-USSR Health Exchange Program and Problem Area 1, the Pathogenesis of Atherosclerosis in Cardiovascular Diseases.

US-USSR Health Exchange Program: Background

The US-USSR program in cardiovascular diseases covers one of the major health areas included in the 5 year agreement between the governments of the United States and the Union of the Soviet Socialist Republics in the field of medical science and public health. Soviet Minister of Health Boris V. Petrovsky and Secretary of State William P. Rogers signed the agreement in Moscow on May 23, 1972.

This agreement represented the culmination of nearly 20 years of contacts and exchanges between medical scientists and physicians of the two countries and reflected the mutual desire for collaboration in areas of health research.

A key element in this agreement, which was not included in earlier cooperative programs, is the mutual planning and execution of joint research activities in both countries according to an organized work plan and common protocols. A second important innovation of the new program is the provision that the mutual cooperation take place directly between specific health institutions in the United States and the Soviet Union. Thus, the National Heart, Lung, and Blood Institute of the National Institutes of Health in Bethesda, Maryland is designated to collaborate with its counterparts, the USSR Academy of Medical Sciences, the A. L. Myasnikov Institute of Cardiology (now the All-Union Cardiological Research Center) in Moscow and the N. N. Anitchkov Department of Athero-

* This paper is also being published in the Russian cardiologic journal *Terapevticheskii arkhiv* (*Therapeutic Archives*).

† For a more complete list of participants in the Study, see the Appendix.

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sclerosis of the Institute of Experimental Medicine in Leningrad.

Earlier exchanges of delegations had been for brief periods, consisting largely of visits to various medical institutions in specialized fields of research. These exchanges formed the necessary framework of understanding and friendship on which the far-ranging formalized current agreement is based. From what had been an occasional method of communication has arisen a carefully delineated approach that calls for the annual submission of progress reports and proposed plans to the Joint US-USSR Committee for consideration and coordination.

The co-chairmen of the US-USSR Joint Committee for Health Cooperation, which first met in Moscow in March 1972, are Drs. Theodore Cooper, assistant secretary for health, Department of Health, Education, and Welfare, Washington, D.C. and Dmitri D. Venedictov, deputy minister of health, Bureau of International Affairs and Personnel, Moscow.

Problem area 1 (Pathogenesis of atherosclerosis): The cooperative efforts now cover five broad areas (cardiovascular disease, cancer, environmental studies, arthritis and influenza and acute respiratory disease); specific problem areas are defined under each heading. The problem areas outlined in cardiovascular disease include: (1) pathogenesis of atherosclerosis, (2) management of ischemic heart disease, (3) myocardial metabolism, (4) congenital heart disease, (5) sudden death, and (6) blood transfusion and, under a separate agreement, artificial heart research and development.

To build effective communications between groups in the United States and the Soviet Union, a Joint Steering Committee was established to overview the collaboration within Problem Area 1. Four to five members from each country constitute this committee, which provides technical review of all aspects of the collaborative US-USSR Lipid Research Clinics Study and coordinates the progress of each study phase. The decisions of the Steering Committee are effected with the assistance of an established Working Group. The Working Group is a collaborating multidisciplinary group of scientists from the two countries who are responsible for implementing many of the decisions of the Steering Committee and also for assisting in the training, certification and monitoring of clinic and laboratory procedures (see Appendix).

Lipid Research Clinic Program Overview

The US-USSR Lipid Research Clinics Study is a unique endeavor to conduct a binational multidisciplinary, multiclinic collaborative research program of the metabolism and epidemiology of plasma lipids and lipoproteins as they relate to atherosclerotic disease in total populations. To achieve this goal, 12 Lipid Research Clinics were established, 10 in the United States and 2 in the Soviet Union. These research clinics are directly responsible for providing subject populations, contacting subjects, performing the necessary interviews, physical examinations and laboratory tests, and, in both countries, for forwarding data to the Central Patient Registry and central laboratories in the United States. In the Soviet Union, secondary biochemical tests are carried out in each individual lipid center by methods comparable with those used in the United States.

Each clinic is responsible for establishing a lipid laboratory to provide standardized measurements of lipids and lipoproteins. Each uses common quality control methods and is charged with the responsibility of determining plasma lipids and lipoproteins with a technical measurement error among research clinics no greater than that which would be obtained on measuring replicate specimens within any one clinic.

In addition, each research clinic is to conduct collaborative epidemiologic studies designed to assess the frequency of primary and secondary dyslipoproteinemias, the natural history of these disorders and possible associations between atherosclerotic heart disease, lipids and lipoproteins and other risk factors, such as diet. The epidemiologic studies can be considered comparable because they each proceed from a common standardized protocol. Each clinic is required to select subjects according to approved procedures from a well defined population. The definition of a sampling frame, the performance of a private census, the identification of master lists of the target population and the monitoring of completion rates of subjects screened are all required.

Each research clinic, in addition to a standardized core lipid laboratory, has a standardized exercise electrocardiographic facility. Nutritionists and interviewers at each clinic have received extensive collaborative training in the use of the collaborative data forms and in taking the standard measurements. Once subjects are selected, all the information is collected by certified technicians, who use directly comparable methods. The data include basic demographic information, historical information regarding illness, symptoms and social factors, medical information, electrocardiographic data and a 24 hour dietary recall.

The USSR-US collaboration has progressed to the point where comparability and standardization have been achieved. It is now possible to speak of one study being conducted in replicate by multiple clinics in two collaborating countries. The clinics in North America were chosen to include geographic diversity, so as to provide epidemiologic information for populations residing in different areas within the United States. In addition, the populations cover wide ethnic, occupational and age ranges. Thus, a variety of cross-cultural comparisons will be possible.

Study populations: Table I specifies the sampling frames for each participating clinic. The subjects under investigation in Moscow and Leningrad are men residing in defined areas of the city. The subjects from the United States sampled by place of residence are those residing in Rancho Bernardo, a newly constructed community near San Diego, California; in Columbia, Maryland, a planned new town; the residents of Rich-

TABLE I

The Sampling Frames

The Sampling Frames	Lipid Research Clinic
Adults in occupational and industrial groups	
University employees	Stanford
Northwest Bell Telephone Company	Seattle
Canadian Bell Telephone Company, Dofasco (Steel Foundry), Simpsons Department Store, Eatons Department Store	Toronto-McMaster
Men in defined residential areas	Moscow, Leningrad
Household units in the following communities:	
Columbia, Maryland, East Baltimore, Maryland	Johns Hopkins
Rancho Bernardo, California	La Jolla
Richfield, Minneapolis	Minnesota
Rural counties, Oklahoma	Oklahoma
Rural county, Iowa	Iowa
School children and their parents	
Houston, Texas	Baylor
Princeton School District	Cincinnati

TABLE II

Description of Prevalence Study Populations

Lipid Research Clinic	Description of Study Population	Target Population Size	Sample Population Size
Baylor (01, 02, 03 years)	High school sophomores in middle and high socioeconomic status schools in the Houston Independent School District and their parents	45,000 sophomores plus the parents giving a total of 135,000	2500 sophomore students plus 5000 parents for a total sample of 7500
Cincinnati	Students in grades 1, 3, 5, 7, 9, 11 and 12 enrolled in the Princeton School District and their parents	12,000 students and parents	4000 students and parents of half of these giving a total of 6700 subjects
Iowa	Adults 25–59 years of age residing in Cedar County, Iowa, and certain rural townships of neighboring counties on July 1, 1973	7541 adults 25–59 years of age residing in the designated area	A 100% sample of all adults 25–59 living in the chosen area giving a total of 7541
John Hopkins	East Baltimore: A random sample of all persons residing in 11 census tracts of the East Baltimore area	46,209 persons residing in the 11 census tracts as of January 1972	A random sample of the 11 census tracts to give a total of 3000 eligibles
	Columbia: A random sample of adults and children who are members of the Columbia Medical Plan	23,600 members of Columbia Medical Plan and relatives residing in same household (approximately 94,400 eligibles)	5000 which includes Columbia Medical Plan members and family members (1200 Columbia Medical Plan participants)
La Jolla	A sample of persons 12 years of age or older who are permanent residents of homes in Rancho Bernardo, California, as of August 12, 1972	7755 permanent residents 12 years of age or older residing in home as of August 12, 1972	7755—a 100% sample of all residents 12 years of age or older living in Rancho Bernardo as of August 12, 1972
Minnesota	Adults and children 10–59 years of age residing in 4 census tracts in Richfield, a suburb of Minneapolis	12,466 residents of the 4 census tracts between 10–59 years of age	8748 eligibles in the age range 10–59 years
Oklahoma	Adults 18 years of age and older residing in 5 rural counties	87,322 eligibles 18 years of age or older in the 5 counties	8732—a 10% random sample in each county
Seattle	Employees of Pacific Northwest Bell Telephone Company between 20–65 years of age who work in King County	6135 employees between 20–65 years of age who work in King County	6135—a 100% sample of all employees in King County
Stanford	Stanford University employees between the ages of 26–70	6047 employees between 26–70 years of age	6047—all employees between 26–70
Toronto-McMaster	Employees of Dofasco, Eaton's, Simpson's and Bell, Canada, and family members of 1000 of these employees	20,918 workers employed by the four companies	7000 of the employees plus spouses and children of 1000 of these (total sample = 10,000)
Moscow	Men born 1916–1935 residing in the Oktyabrskii District by 1974 voting lists	25,000 men aged 40–59	5000
Leningrad	Men born 1916–1935 residing in the Petrogradskii District by 1974 voting lists	10,000 men aged 40–59	5000

field, a suburban area in Minneapolis, Minnesota and residents of selected predominantly rural counties in Oklahoma and Iowa.

The research design permits a direct test between comparable populations in the United States and the Soviet Union defined by residential area, age and sex. There also is the opportunity for comparison of men in the Soviet Union with North American populations defined by other criteria, such as industrial or occupational group. Table II presents a more detailed description of each of the Lipid Research Clinic study populations participating in the collaborative study.

Sampling strategy: The sampling strategy for the collaborative Lipid Research Clinic studies is outlined in Table III. Visit 1 is conducted in the clinic and in the subject's home, place of work or school by a team of interviewers and technicians trained in obtaining blood samples. Demographic data are collected as well as information about the current use of five types of medication: drugs to reduce lipids, sugar, uric acid or blood pressure as well as oral contraceptive agents or estrogens. A fasting blood sample is taken for measurement of cholesterol and triglycerides.

A randomly chosen 15 percent of all participants in Visit 1 are invited to Visit 2; in addition, all subjects are invited whose Visit 1 lipid results are above age-specific cutoff points for cholesterol and triglycerides,* or who indicate that they are currently using lipid-lowering drugs. Fasting blood samples are drawn for lipid and lipoprotein quantification and for analysis for other biochemical measurements. Diet and drug histories are taken, and the remainder of the history and physical examination places emphasis on the cardiovascular system. Resting and treadmill stress electrocardiography are performed. Thus, a more in-depth study of the relation of lipid levels to cardiovascular status and the presence or absence of other diseases is undertaken during Visit 2.

The performance of detailed lipoprotein quantification and stress electrocardiography is of such complexity and expense that it was deemed desirable to carry out these procedures in subsets of all examinees, and to collect less expensive basic demographic and

* For comparative purposes, the cutoff points used in the United States are also used in the Soviet Union.

TABLE III

The Sampling Strategy

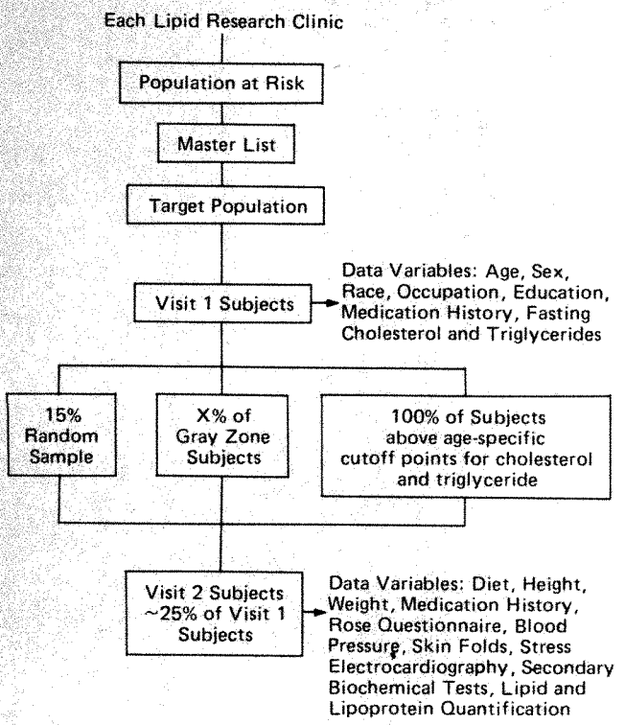


TABLE IV

Purpose of Lipid Research Clinic Study

The Lipid Research Clinics Program will describe the distribution of plasma lipids and major lipoprotein fractions in a wide variety of populations.

This description will be both quantitative and qualitative; i.e., the lipids and lipoproteins will be analyzed both as continuous graded characteristics and as discrete, categorical entities, i.e., phenotypes.

The major population determinants of lipid and lipoprotein distributions and their sequelae will be assessed by studying their association with:

Personal characteristics
- Age, sex

Ethnicity and race

Social characteristics
- Occupation
- Education
- Socioeconomic status

Anthropometry
- Height, weight
- Body mass indexes, i.e., Quetelet index
- Skinfolds

Diet

Physical fitness

Atherosclerotic diseases
- Angina
- Myocardial infarction
- Peripheral vascular disease

Co-morbidity
- Diabetes
- Hypo- and hyperthyroidism
- Serum uric acid disorders

lipid information in the total study population. For this reason, the procedures were divided into Visit 1 and Visit 2 examinations. As indicated in Table II, the number of subjects examined to date in each of these procedures is in excess of 70,000 for Visit 1 and 15,000 for Visit 2. Visit 2 subjects include both a random sample of Visit 1 examinees, and therefore representative of the target population, and also a 100 percent sample of all subjects found to have hyperlipidemia at Visit 1. For the purpose of this first collaborative publication, attention will be focused primarily upon Visit 1 procedures.

Aims of the study: Table IV sets out the general purposes of the Lipid Research Clinics Prevalence Study. In addition to the general purposes, we call attention to the more directly and immediately important specific questions and hypotheses under investigation in this collaborative USSR-US activity. These are as follows:

1. To test for, measure and describe the similarities or differences in plasma lipid and lipoprotein values across populations in the Soviet Union and the United States.
2. To identify, in as much detail as possible, the demographic and physiologic factors associated with hyperlipidemia and dyslipoproteinemias and to capitalize on the cross-national nature of our study to identify any similarities or differences in the determinants of plasma lipid or lipoprotein abnormalities.
3. To investigate the associations of hyperlipidemia with various physiologic and demographic characteristics of the population studied, and their joint association with coronary heart disease. Given the common sampling protocol and the standardization of procedures, we shall have an almost unique opportunity to test for cross-national similarities and differences, if any, in the association of hyperlipidemia with coronary disease.
4. As an example of the points made in Item 3 above, the detailed study of the epidemiology of dietary surveys and resting and exercise electrocardiography will be described in these cross-national studies and the universality of their relations to coronary heart disease tested.

Common Methods and Standardization Procedures

This section will not present detailed, definitive results of a scientific nature, but rather illustrative examples of the achievements of collaboration. This procedure is followed for two reasons: first, because it is the purpose of this paper to present an overview and not to review in detail all the findings; and second, because the data are still in the process of collection and, hence, can only be preliminary. The following illustrative examples of collaboration will be presented:

1. Agreement of the common collaborative definition of the sampling frames. As seen in Table II, the collaborative definition of the sampling frame has been achieved and for many of the clinic populations, direct comparability of the epidemiologic results in the two countries is now possible.

2. Achievement of standardization of procedures. Most of the procedures used for data collection have been successfully standardized through training and practice regimens. For example, the lipid standardization program of the Center for Disease Control in the United States is used to standardize lipid measurements at all clinics. This program is divided into an evaluation phase (Phase I), a standardization phase (Phase II) and

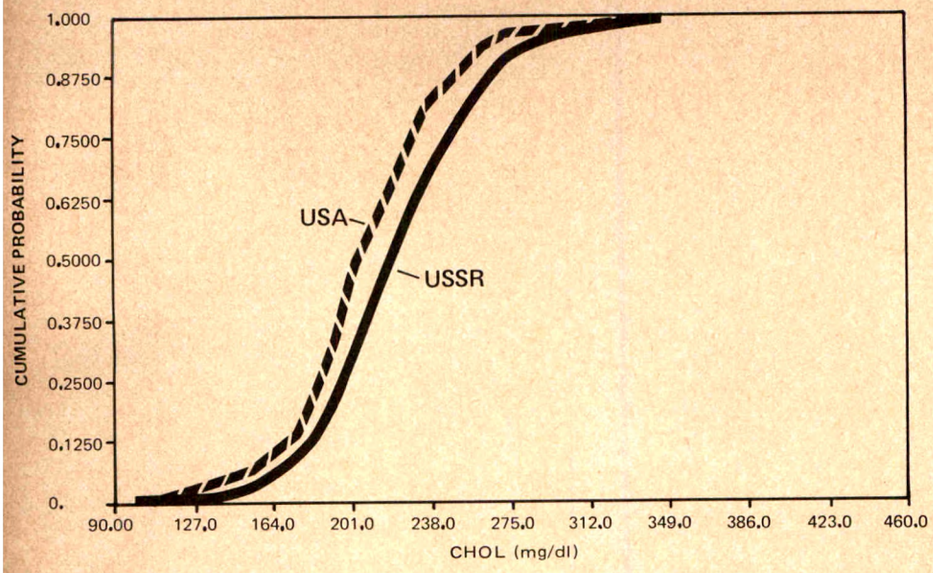


FIGURE 1. Empirical distribution of total plasma cholesterol (CHOL). Men aged 40 to 49 years.

a surveillance phase (Phase III). In Phase I, the precision and accuracy of lipid analysis are established by analyzing 120 samples in a period of 2 to 4 weeks. Phase II provides a more intensive evaluation to determine precision and accuracy over a longer period of time. It involves 32 analyses of 320 samples during 8 to 16 weeks. Successful completion of Phase II results in laboratory "standardization." The surveillance phase (Phase III) provides a continuous check of performance after standardization. Six samples are analyzed 1 day/week for the duration of the program.

3. Certification of personnel. To ensure some minimal level of performance in the program, certain personnel are certified in the performance of standardized procedures. These include persons responsible for taking blood pressure, persons responsible for administering the Rose questionnaire, cardiologists or technicians responsible for producing electrocardiographic tracings and dietary interviewers.

As an illustration, persons taking blood pressure must study a training manual, observe a training film on recognition of systolic and diastolic phase V pressures and use tape recordings of 12 sets of Korotkoff sounds to practice recognition of these blood pressure levels. When they have demonstrated satisfactory performance on the practice tape recordings, the final step in certification requires that average systolic and diastolic phase V readings for a second group of 12 sets of Korotkoff sounds come within 1 second (2 mm) of the correct average. An audiogram is also administered to all trainees.

Illustrative Preliminary Survey Results

This section reports selected data from the epidemiologic surveys in the Soviet Union and the United

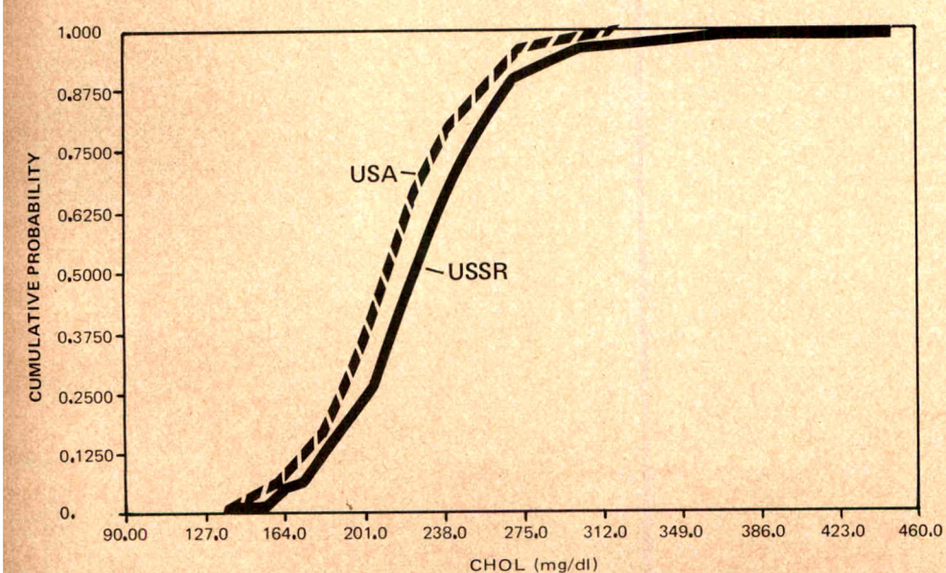


FIGURE 2. Empirical distribution of total plasma cholesterol (CHOL). Men aged 50 to 59 years.

States. The lipid and lipoprotein distributions presented illustrate the progress made in collaborative research programs, but the data should be considered preliminary and may not reflect final results. At the time of this report the clinics in both countries are still screening subjects; however, comparative data have been chosen from similar points in the history of each study and should reflect values for men aged 40 to 59 years residing in the specified target areas identified in Table I. Data are presented for 992 men in the Soviet Union and 629 subjects of comparable age in the United States.

Plasma cholesterol: Figure 1 displays the full frequency distribution of fasting total plasma cholesterol in men aged 40 to 49 years in the two national samples. Table V presents selected summary statistics of these full frequency distributions. Total plasma cholesterol levels are higher in the Soviet than in the North American sample. The difference is approximately 10 to 13 mg/dl, as reflected in the mean and median values; however, the total distribution of Soviet values appears displaced toward higher values.

For both samples there is a slight increase, approximately 4 mg/dl, in total plasma cholesterol between the 5th and 6th decades of life. The general shape of the curves for the age group 50 to 59 years is similar to that described for the age group 40 to 49 years (Fig. 2).

Plasma triglycerides: Figure 3 displays the distribution of total plasma triglycerides in men aged 40 to 49 years and Table V presents selected summary statistics. It is apparent that there are marked differences in the distribution of plasma triglycerides in these two samples, the selected North American subjects having fasting levels approximately 25 mg/dl higher, as re-

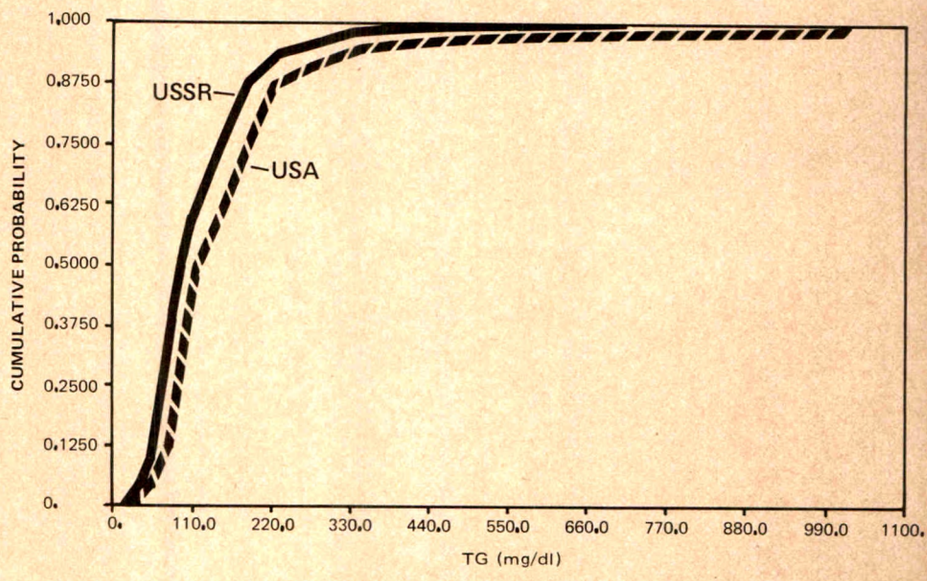


FIGURE 3. Empirical distribution of plasma triglycerides (TG). Men aged 40 to 49 years.

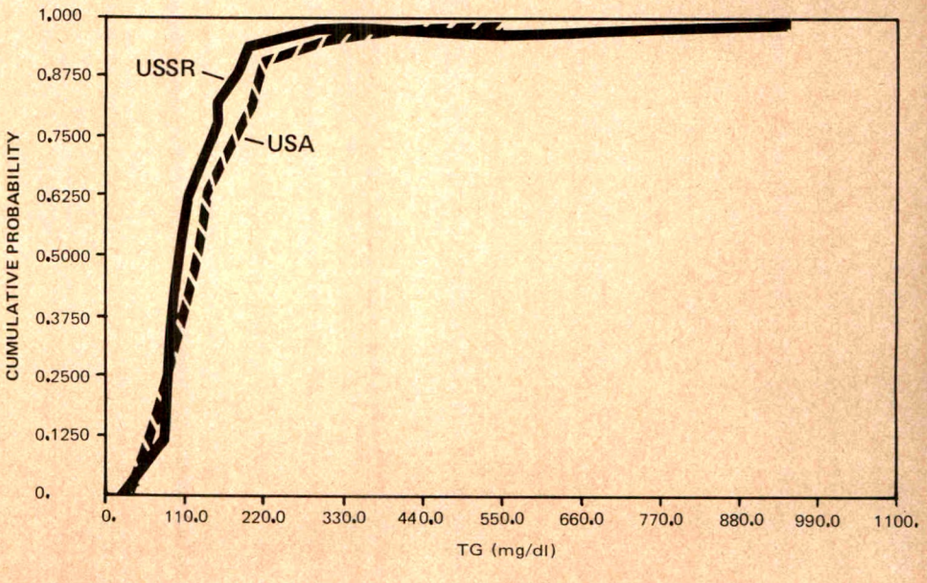


FIGURE 4. Empirical distribution of plasma triglycerides (TG). Men aged 50 to 59 years.

TABLE V

Distribution Comparisons Between the US and USSR Samples

	Maximum (mg/dl)	Minimum (mg/dl)	Median (mg/dl)	DMAX*	P_{val}†
Age Group 40 to 49 Years					
Cholesterol					
US	337	98	206	0.154	$P_{val} < 0.001$
USSR	362	105	219		
Triglycerides					
US	1020	32	112	0.124	$0.001 < P_{val} < 0.005$
USSR	711	31	100		
HDL cholesterol					
US	96	19	45	0.271	$P_{val} < 0.001$
USSR	181	23	53		
Age Group 50 to 59 Years					
Cholesterol					
US	318	139	212	0.143	$0.001 < P_{val} < 0.005$
USSR	450	134	222		
Triglycerides					
US	2106	39	117	0.122	$0.01 < P_{val} < 0.025$
USSR	937	36	104		
HDL cholesterol					
US	106	18	47	0.179	$P_{val} < 0.001$
USSR	122	24	51		

* DMAX = $\max_x |F_{n_1}(x) - F_{n_2}(x)|$ where F_{n_1} (US) (x) and F_{n_2} (USSR) (x) are the empirical functions of lipid variable x for the US and USSR samples of size n_1 and n_2, respectively.

† P_{val} = the probability of rejecting H_0: F (US)$_{(x)}$ = F (USSR)$_{(x)}$ under the assumption that H_0 is true, using the two sample Kolmogorov-Smirnov test.

flected in both the mean and the median values. For each sample there is evidence of marked skewing toward higher values. Generally similar results are present for men aged 50 to 59 years although the differences between the national samples are somewhat less, the North American values averaging approximately 13 to 15 mg/dl higher than the Soviet values (Fig. 4).

High density lipoproteins: A local modification of the collaborative Lipid Research Clinics protocol by the Soviet clinics has allowed their collection of information on high density lipoproteins during Visit 1. This analysis was not generally performed during Visit 1 in the United States although it was obtained for at least 629 men who attended the clinics in the United States early in the course of the study. These values were used to assist in the design of the US Coronary Primary Prevention Trial. Because the values come from men of a comparable age and from a comparable stage in the course of the study as in the Soviet study, it was believed that a comparative analysis could be presented.

The full distribution of plasma high density lipoprotein cholesterol in men aged 40 to 49 years in the Soviet and North American samples is presented in Figure 5 and for men aged 50 to 59 years in Figure 6. Selected summary statistics are presented in Table V. For men aged 40 to 49 years an 8 to 10 mg/dl difference between the two samples is apparent, as reflected in the mean and median values, with the Soviet plasma high density lipoprotein cholesterol levels being higher. As for total cholesterol, there is a suggestion that the Soviet data are skewed toward higher values than the North American data.

In spite of the selected nature of the samples, the lipid and lipoprotein measurements are comparable among countries and across clinics. Laboratory quality control, standardization and monitoring have assured this comparability. Attention is called particularly to the lipoprotein quantification. Duplicate specimens have been tested both in the Soviet Union and in the United States, with comparison of electrophoretic patterns. The differences reported appear not to be due to laboratory differences.

Implications: The comparative data presented therefore demonstrate the feasibility of planning, implementing and administering large scale epidemiologic studies of lipid and lipoprotein patterns in free-living populations across nations using common protocols and standardized measurements. Computer processing has been centralized at the Central Patient Registry, resulting in the generation of the comparative lipid distributions displayed in Figures 1 to 6.

If the selected samples reported in this preliminary set of data are representative of the total target populations, there will be the interesting demonstration of

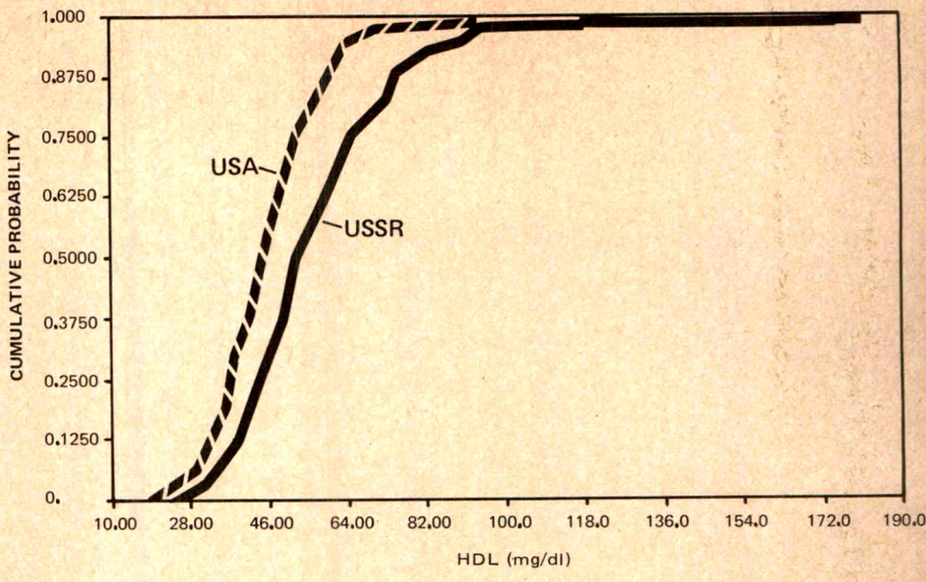


FIGURE 5. Empirical distribution of high density lipoprotein (HDL) cholesterol. Men aged 40 to 49 years.

major differences in lipid and lipoprotein distributions across these populations. The suggestion is that, for middle-aged men, levels of total plasma cholesterol and high density lipoprotein cholesterol are significantly higher and triglycerides significantly lower in the Soviet Union than in the United States. We will be in a position to analyze these differences in lipid and lipoprotein distributions between countries in relation to demographic, medical and other salient characteristics and to study their relation to coronary heart disease.

Conclusions

The experience reported here may well be unique in its demonstration of international planning and the consequent collection, analysis and exchange of standardized, population-based biomedical data. This achievement was made possible, to a great extent, by effective interpersonal relations built among the collaborating scientists, senior administrators and staff personnel. It is also due to the expenditure of considerable time, effort and energy in research planning and administration. Many challenges caused by the geographic distances among the participants, problems of language and, at the outset, differences in basic scientific and communication technology were met and addressed. One major achievement has been the establishment of working cross-national communication among colleagues in the fields of biostatistics, biochemistry, epidemiology, cardiology, electrocardiography and nutrition.

As the preliminary results illustrate, cooperative programs of this kind can progress beyond rhetoric and lead to meaningful and productive collaboration. The experience has demonstrated that such studies are exportable and can be adapted successfully to disparate

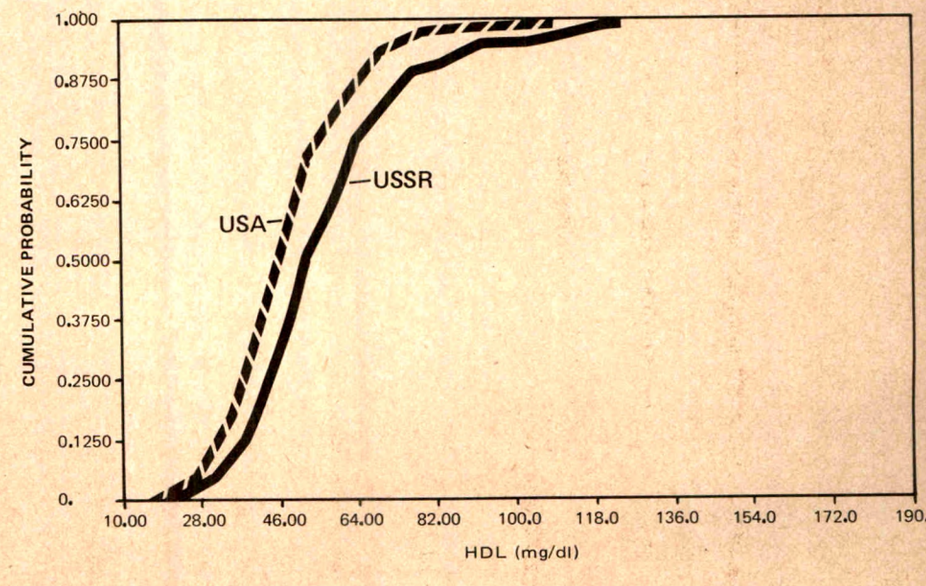


FIGURE 6. Empirical distribution of high density lipoprotein (HDL) cholesterol. Men aged 50 to 59 years.

social, ethnic and techologic conditions while preserving the standardization and comparability criteria essential to scientific validity.

In conclusion, the US-USSR Agreement in Health has provided an appropriate framework for communication among the scientists of both countries. Programs in the specific problem area described are functioning well as a result of the effective communications network established through both the formal committee structure and the informal contacts among individual scientists at all levels. Moreover, the agreement has promoted collaboration between the scientific communities and the governments of two nations, and has shown that this can be a viable and operative tool in joint planning of research. In this instance, it was possible to identify common problems, establish mutual priorities and agree on bilateral ways of investigating potential solutions. Thus, scientists can help formulate and governments can help support practical proposals intended to preserve rather than destroy humanity.

APPENDIX

US-USSR STEERING COMMITTEE

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Diagnosis of Myocardial Infarction: Historical Notes From the Soviet Union and the United States

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Boston, Massachusetts

Soviet physicians attribute the first description of the clinical presentation of a nonfatal myocardial infarction to V. P. Obraztsov and N. D. Strazhesko; American physicians attribute the same achievement to James B. Herrick. Investigation of the origins of the conflicting claims reveals that the Russian physicians published an accurate account of the syndrome in 1910. Herrick, in his article published in 1912, cites a German translation of the Russian article. Herrick's major contribution consisted of informing American physicians of the symptoms of infarction, and stimulating development of the electrocardiogram as a diagnostic aid.

The growing contact between the physicians of the Soviet Union and the United States has revealed a major difference in medical history. American physicians refer to James B. Herrick[1] as the first to describe the clinical presentation of a nonfatal myocardial infarction; Soviet physicians attribute the same achievement to V. P. Obraztsov and N. D. Strazhesko.[2] It is of great interest to trace these conflicting claims to their origins, not to satisfy the urgings of a narrow nationalism, but to unravel the intellectual history of a major advance in clinical medicine.

Obraztsov and Strazhesko

The Soviet tradition is based on the paper "K Simptomatologii I Diagnostike Tromboza Venechnikh Arterii Cerdtsa" (On the Symptomatology and Diagnosis of Coronary Thrombosis),[2] published in 1910, two years before the paper by Herrick.[1] The article of Obraztsov and Strazhesko begins with a discussion of the conventional wisdom of the era regarding coronary thrombosis. Coronary thrombi were well known to pathologists, but clinicians of that day thought that they led to sudden death or failed to produce symptoms of any kind. Cohnheim, a prominent experimentalist of the mid-19th century, had occluded the coronary arteries in a group of dogs; all of the dogs died within 2 minutes of the occlusion. This experiment and Cohnheim's influence led to general acceptance of the idea that sudden death was the only symptom of coronary occlusion.

The Russian authors[2] quote investigators who found results contrary to those of Cohnheim and then indicate their intent "to focus on the clinical picture and diagnosis of occlusion of the coronary arteries producing a moderately extensive myocardial infarction." They present five cases of myocardial infarction, three of which were confirmed by autopsy findings. The first case was described as follows:

Case 1: G.E. A 49 year old artillery man was admitted to the medical division of the Aleksandrovsky Hospital on December 5, 1899. For 12 days prior to admission, he had experienced substernal pain radiating to the throat, head and left arm. The attacks lasted 2 to 4 hours and after a brief pause would begin again. During the attacks he experienced shortness of

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FIGURE 1. A photograph of Vasilii Parmenovich Obraztsov (circa 1910) published in 1949 in Klinichaskaya Meditsina[3] on the 100th anniversary of his birth.

breath and the inability to breathe deeply. The chest pain was so severe that the intern on my service, who was young and inexperienced, in response to my question as to the patient's admitting diagnosis responded "rheumatism of the chest."

Objective Findings: He was well nourished and well developed. There was moderate cyanosis of the mucous membranes. His facial expression revealed distress from the substernal pain which radiated to the neck and head. No vessel motion was visible in the neck. The respiratory and abdominal organs were without abnormalities. The cardiac impulse was not visible, but was weakly palpable in the 5th intercostal space in the left mammary line. The heart sounds were distant and there were no murmurs. Direct auscultation revealed presystolic splitting of the first sound. Pulse 90 and barely palpable. Rhythm regular. *After the initial examination the diagnosis of coronary thrombosis was made.*

The patient died 4 days later on December 9, 1899.

Autopsy Findings: On cross section of the left ventricle its entire thickness was of a muddy-gray yellowish color, as seen with necrosis. These changes occurred in almost the entire wall of the left ventricle and septum.

Near the origin of the right coronary artery there was a 1 cm long yellowish projection from the wall of the vessel producing some luminal narrowing. The changes in the left coronary were more severe. The left anterior descending coronary artery was occluded by grayish-red thrombus 1 cm long and 1 mm in diameter. The left circumflex was occluded by a 3 cm long soft yellow thrombus.

On the basis of this case history and others, Obraztsov and Strazhesko drew the following general conclusions about myocardial infarction:

All patients noted an acute, sudden onset of the disease. Direct events often precipitated the disease; the infarct began in one case on climbing a high staircase, in another during an unpleasant conversation and in a third during emotional distress associated with a heated card game. Consciousness remained clear in all patients. Subjective complaints were of 3 types:

1) Substernal pain with radiation to the neck, head and left hand (cases 1 and 3);
2) Shortness of breath or dyspnea, reaching such a severe degree that it did not permit the patient to lie or sleep (orthopnea);
3) A feeling of heaviness and severe pressure in the epigastrium and about the heart, which in some cases limited respiration.

In general, the objective signs indicated a severe decrease in myocardial function.

The differential diagnosis of coronary thrombosis from angina pectoris is made by the presence of status anginosus with coronary thrombosis and its absence with isolated attacks of angina pectoris. Although cardiac dysfunction occurs with angina pectoris, in the presence of coronary thrombosis, it does not remit with the termination of an angina attack but persists quosque ad finem vitae.

As is often the case, this perceptive achievement was not an isolated triumph in the life of an individual. V. P. Obraztsov was born in 1850 and received his medical education in St. Petersburg.[3] In 1893, he was named professor of Pathology and Therapeutics at the University of Kiev and became chief of the Department of Therapeutics in 1904 (Fig. 1). He taught many students, among them N. D. Strazhesko, who later occupied academic positions.

Obraztsov's early academic interests centered around the physical diagnosis of abdominal disorders. He devised a classification system for appendicitis and a palpation system that bears his name. In the cardiovascular area, he described changes in the heart sounds with direct auscultation and the association of a gallop rhythm, not only with hypertrophy, but with loss of heart muscle from any cause. Through periodic visits to the laboratory of Virchow and those of other European leaders of medicine of the 19th century, he remained in contact with the most advanced medicine of the time. It therefore is not unusual that such a man would be in a position to make an original contribution to the advance of medical knowledge.

James B. Herrick

Herrick's article,[1] which appeared in 1912, is generally quoted by American physicians as the first complete description of the syndrome of myocardial infarction. However, Herrick was careful to indicate his familarity with a German translation of the publication by Obraztsov and Strazhesko.[4] Like the Russians, he began with reference to the dogma of Cohnheim that occlusion of a major coronary artery was immediately fatal. He followed this with laboratory and clinical observations indicating the existence of collateral vessels and the possibility of survival after coronary occlusion. Herrick then presented the case history of two patients with the syndrome of myocardial infarction, one of whom had a

coronary thrombosis demonstrated at postmortem examination. The primary importance of Herrick's work was its widespread effect on the concept of coronary occlusion during that period of American medical history.

Herrick's contribution was also not an isolated achievement. He, too, was a distinguished teacher and researcher active in many fields of internal medicine.[5] In the field of hematology he gave the red cells that he observed in cases of sickle-cell anemia their distinctive name.[6] Because of his interest in myocardial infarction, he stimulated the development of the electrocardiogram for assistance in diagnosis of the disease. Finally, in the conclusion of his article he presented a logical approach to the treatment of a patient with myocardium in the process of infarcting. "The hope for the damaged myocardium lies in the direction of securing a supply of blood through friendly neighboring vessels so as to restore as far as possible its functional integrity." With this statement he anticipated by more than half a century the great interest in limitation of infarct size which began several years ago.

In summary, widespread recognition of the clinical presentation of myocardial infarction required astute clinical observation and effective communication of the description of the disease within each country. The first complete description of the disease was presented by Obraztsov and Strazhesko in 1910. Herrick described the disease for American physicians in 1912, stimulated the development of the electrocardiogram for its diagnosis and correctly prophesied an approach to therapy that has only recently been rediscovered.

Acknowledgment

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Echocardiographic Features of Right Ventricular Outflow Tumor Prolapsing Into the Pulmonary Artery

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The echocardiographic features of a tumor in the right ventricular outflow tract that prolapsed into the pulmonary artery during systole are described. The patient was a 19 year old woman who presented clinically with bacterial endocarditis involving a mildly stenotic pulmonary valve. An echocardiogram, obtained to evaluate the pulmonary valve for bacterial vegetations, showed abnormal echoes throughout the cardiac cycle; they suggested a tumor mass in the right ventricular outflow tract in front of the pulmonary valve with possible extension into the pulmonary artery during systole. Additional tumor echoes confined to diastole were recorded in front of the aortic root and the tricuspid valve. These features were further elucidated with a computer-generated two dimensional cineechocardiogram that clearly showed a portion of the tumor mass passing beyond the position of the pulmonary valve into the main pulmonary artery in systole and returning into the right ventricular outflow in diastole. At surgery, a large myxoma was found in the right ventricular outflow tract with a polypoid extension that projected into the pulmonary artery in systole and contained a fibrinous vegetation at its tip. The left cusp of the pulmonary valve was normal, but the other two leaflets showed evidence of endocarditis.

Cardiac tumors are commonly found in the left atrium, and many reports[1–8] have dealt with their ultrasonic detection in this region. Because right-sided tumors are rare, their echocardiographic observation has been relatively infrequent.[5,9–14] In this report we describe the echocardiographic fatures of a tumor in the right ventricular outflow tract, a portion of which protruded into the pulmonary artery during systole and descended into the right ventricle during diastole.

Case Report

A 19 year old woman was admitted to The Genesee Hospital with a 5 day illness of malaise, fever, generalized weakness and night sweating. There was no past history of rheumatic fever, but examination 1 year before admission had revealed a heart murmur.

On physical examination the pulse rate was 96/min and regular and the blood pressure was 110/70 mm Hg. The apical impulse was normal as were the first and second heart sounds. There was a grade 3/6 systolic ejection murmur preceded by a right-sided ejection click as well as a grade 1/6 low-pitched early diastolic murmur heard in the second left intercostal space. No other diastolic sounds were audible. The chest roentgenogram was within normal limits. The electrocardiogram showed a tall R wave in lead V_1 compatible with right ventricular hypertrophy. The erythrocyte sedimentation rate (Westergren) was 60 mm in 1 hour and blood cultures were positive for alpha hemolytic streptococcus.

The clinical diagnosis was bacterial endocarditis probably involving a mildly stenotic pulmonary valve with valve incompetence. The patient was treated for 4 weeks with penicillin and streptomycin and responded to therapy but the

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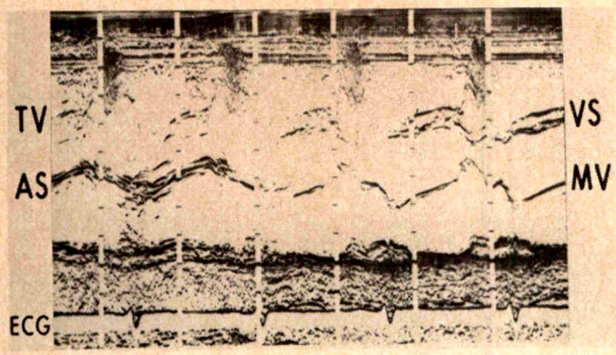


FIGURE 1. Tricuspid-mitral beam sweep. In the tricuspid beam position (**left**) tumor echoes occur during diastole in front of the tricuspid valve (TV), but none pass into the right atrium during systole. The right ventricular position of the tumor is emphasized as the beam is directed toward the mitral valve (MV). AS = atrial septum; ECG = electrocardiogram; VS = ventricular septum.

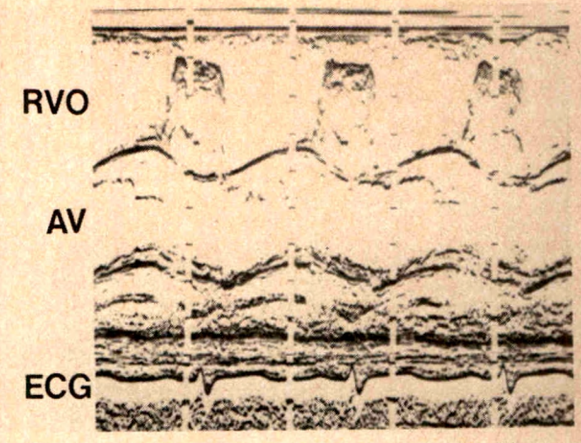


FIGURE 2. Aortic root recording. Tumor echoes confined to diastole are present in the right ventricular outflow tract (RVO). AV = aortic valve; ECG = electrocardiogram.

murmurs did not change. Eight blood cultures taken after antibiotic therapy were sterile, but the erythrocyte sedimentation rate remained high (approximately 35 mm in 1 hour).

Echocardiogram: To evaluate the pulmonary valve for bacterial vegetations, echocardiography was performed during the course of antibiotic therapy. Survey of the tricuspid valve revealed abnormal echoes suggestive of a tumor in the right ventricular cavity in front of the tricuspid valve in diastole, but no abnormal echoes were observed in the right atrial cavity behind the closed position of the tricuspid valve or in the vicinity of the interatrial septum.[15,16] Moving the ultrasonic beam from the tricuspid to the mitral valve revealed further evidence during diastole of echoes of a right ventricular mass (Fig. 1). The right ventricular cavity and outflow tract appeared to be enlarged and tumor echoes were present in the right ventricular outflow tract anterior to the aortic root and were confined to diastole (Fig. 2). Examination of the pulmonary valve (Fig. 3) demonstrated a bizarre multilinear rapidly moving mass of echoes in the right ventricular outflow tract anterior to the pulmonary valve leaflet, which appeared structurally normal. Clear extension of the abnormal echoes into the pulmonary artery could not be recognized in these M mode studies although a few abnormal echoes moved posteriorly as the valve opened. When the beam was angled in the region of the pulmonary valve to detect the greatest range of motion of the abnormal echoes (Fig. 4), the pulmonary valve was not seen but the study revealed two rapidly moving thick linear echoes that moved anteriorly in diastole and posteriorly at the onset of systole as well as a thick band of abnormal echoes with a much smaller range of motion and coarse undulations confined to systole.

A computer-generated two dimensional cineechocardiogram using a previously described electrocardiographic gating principle[17] was obtained in a plane that was parallel to the left sternal border and passed through the right ventricle, right

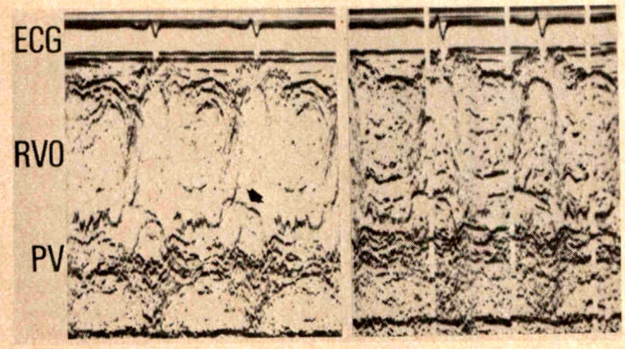


FIGURE 3. Pulmonary valve recording. The pulmonary valve (PV) (**arrow**) lies posteriorly in a widened right ventricular outflow space (RVO) and appears structurally normal (**left**). Tumor echoes are present in the outflow tract and demonstrate wide excursions with the cardiac cycle. With increased gain (**right**) tumor echoes follow the pulmonary leaflet during systole suggesting that the mass passes into the pulmonary artery. ECG = electrocardiogram.

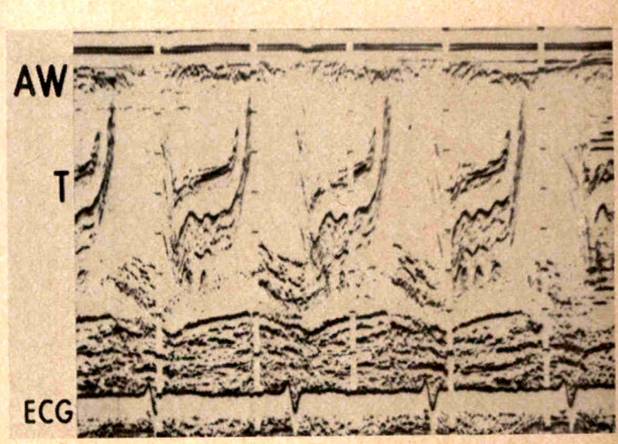


FIGURE 4. Tumor mass recording. The beam was directed in a manner similar to that used for pulmonary valve recording. The wide band of echoes (T) seen partially during diastole and more completely during systole probably arise in the main tumor mass while the rapidly moving components with large excursions may represent the polypoid extension from the main mass. AW = anterior right ventricular wall; ECG = electrocardiogram.

ventricular outflow tract, pulmonary artery and left ventricle (Fig. 5). A mass of abnormal echoes with a roughly spherical shape was identified in the right ventricular outflow tract just below the pulmonary valve. These echoes had a limited range of motion, descending into the upper right ventricle in diastole and moving toward the pulmonary valve but not into the pulmonary artery in systole. In addition, a smaller rapidly moving echo complex, probably connected to the main mass, was seen at a higher level moving into the main pulmonary artery during systole and into the right ventricular outflow tract during diastole. The pulmonary valve leaflet appeared to move normally.

Right heart cineangiograms (Fig. 6) obtained with use of a catheter placed in the superior vena cava, showed a large tumor mass in the right ventricular outflow area moving superiorly toward the pulmonary artery during systole.

Surgical findings and results: A myxoma measuring 5 by 4 by 2 cm was located in the right ventricular outflow tract and attached by a short stalk (1 by 0.5 cm) to the anterolateral wall of the infundibulum (Fig. 7). Two polypoid projections on the tumor mass each measured about 2.5 cm in length and 1 cm in maximal thickness. One contained a soft fibrinous vegetation at its tip and was noted to project into the main pulmonary artery in systole. The anterior cusp of the pulmonary valve had a central perforation; the right cusp was almost completely destroyed with bacterial endocarditis whereas the posterior (left) cusp appeared to be normal. Both the ven-

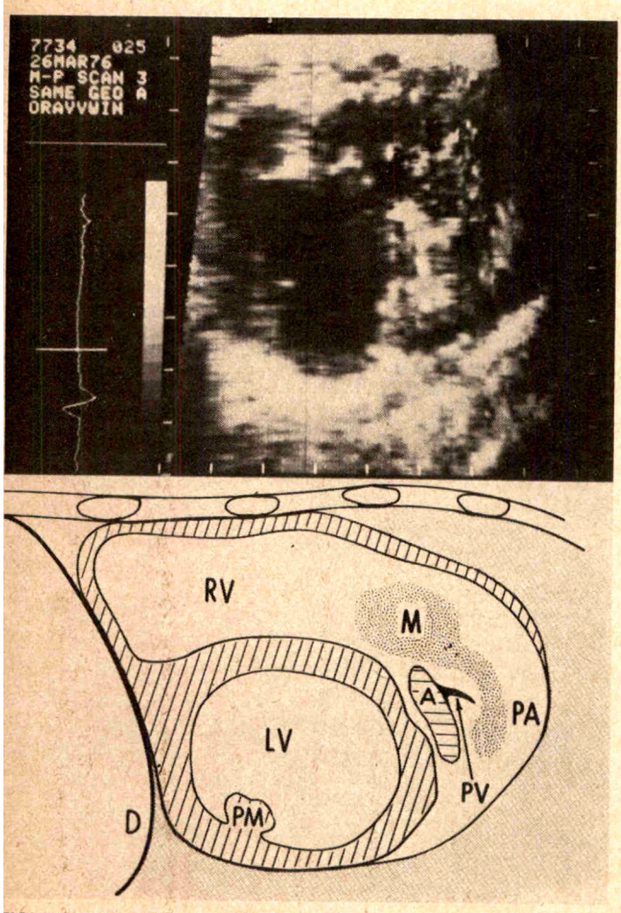


FIGURE 5. Two dimensional echocardiogram (**above**) and a schematic cross section (**below**) demonstrates the position of the mass (M) and shows the relationship of cardiac structures. During systole the main mass is in the outflow portion of the right ventricle adjacent to the pulmonary valve (PV) with extension into the main pulmonary artery (PA). In motion, the prolapsing segment of the tumor flipped rapidly between the right ventricle in diastole and the pulmonary artery during systole. Local enhancement of the brightness of the main tumor mass was provided by computer processing of the image. A = left atrial appendage; D = diaphragm; LV = left ventricle; PM = papillary muscle; RV = right ventricle.

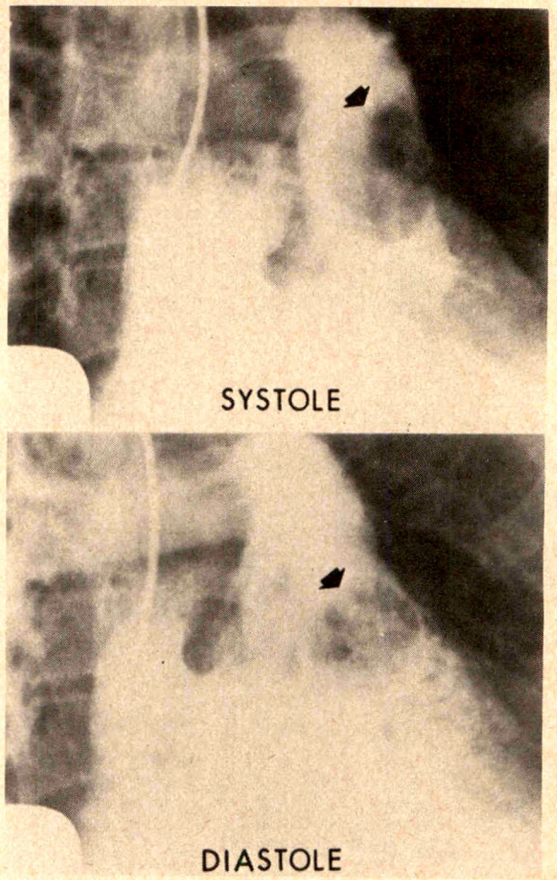


FIGURE 6. Right heart angiogram. **Lower panel,** during diastole. The filling defect (**arrow**) represents the tumor mass in the outflow tract of the right ventricle. **Upper panel,** during systole. The tumor mass (**arrow**) moves superiorly toward the pulmonary artery.



FIGURE 7. Surgical specimen of the multilobed myxoma. The **arrow** points to a polypoid extension that showed evidence of endocarditis at its tip. At operation, this portion of the tumor was noted to extend into the pulmonary artery during systole. A portion of the resected right ventricular wall and a short stalk are indicated by S.

tricular septum and tricuspid valve were normal. The tumor together with its stalk and a small portion of the right ventricular wall were resected.

Since surgery, the patient has remained asymptomatic and has returned to work. The first heart sound is normal and the second heart sound is soft and appears to be single. There is a systolic ejection click in the pulmonary area with a prominent third heart sound. There is now a soft murmur of pulmonary insufficiency although initial follow-up revealed no audible heart murmur.

A repeat echocardiogram has shown complete disappearance of the abnormal echo complexes.

Discussion

Echocardiography is an established procedure for diagnosing cardiac tumors, most of which are myxomas. These tumors are readily identified by the presence of an abnormal grouping of echoes occurring in multiple punctate signals or in continuous wavy parallel lines. The location and pattern of motion of these echo masses are determined by the site of attachment, physical size and mobility of the tumors in various phases of the cardiac cycle.[1–8] Large atrial tumors are characteristically detected as echo masses prolapsing in the ventricular inflow tract with the opening of the atrioventricular valve during diastole and returning into the atrium during systole. A right atrial tumor that prolapses into the right ventricle may also present as a localized diastolic band of echoes anterior to the ventricular septum as well as in the right ventricular outflow tract in front of the aortic root[18] (Dashcoff et al., unpublished data). In the only reported ultrasonic study of a right ventricular outflow myxoma,[19] a cloud of echoes was observed throughout the cardiac cycle anterior to the aortic root; this finding, together with the absence of echoes in the right atrial cavity behind the tricuspid valve, served to differentiate the tumor from a large prolapsing right atrial myxoma. The tumor was attached to the septal leaflet of the tricuspid valve and adjacent ventricular septum; the pulmonary valve, which was not recorded, was apparently not involved.

In our patient M mode echocardiographic studies of the pulmonary valve proved essential in determining the site of attachment and mobility characteristics of the tumor. The location of the tumor in the right ventricular outflow tract was suggested by the delineation of abnormal echoes throughout the cardiac cycle in front of the image of the pulmonary cusp because this space represents the outflow tract immediately beneath the pulmonary valve.[20] Systolic prolapse of the tumor into the main pulmonary artery was suspected from the presence of abnormal although scattered and inconstant echoes in the lumen of the vessel imaged beyond the plane of the pulmonary valve during systole[20] (Fig. 3). The two dimensional echocardiogram clearly showed a portion of the mass passing beyond the position of the pulmonary valve into the main pulmonary artery and returning into the right ventricular outflow tract during diastole. It also allowed a more complete appreciation of the complex motion pattern of the tumor, which was incompletely shown in the M mode records because the mass left the beam in some portions of the trajectory.

The true size of the mass was not clearly delineated in either the M mode or the two dimensional studies. This defect was probably caused by the specular nature of the reflecting surfaces, which caused some image dropout, as well as the selection of direction of the beam or plane.

Differentiation of right ventricular and right atrial tumors: Although the lack of abnormal echo complexes behind the closed position of the tricuspid valve suggested that our patient's tumor did not originate in the right atrium, it is often difficult to identify the chamber of origin. Reverberations produced in a right ventricular tumor mass may be imaged in a position posterior to the tricuspid valve but their true nature may be established by using multiple beam angles to exclude systolic tumor echoes in the right atrial cavity. We have also detected layered echo complexes behind the tricuspid valve during systole in normal subjects. These are probably reverberation artifacts that can be differentiated from tumor masses because they do not move in the direction of blood flow. Also, they are not readily reproducible when the angle and position of the beam are changed.

Tumor echoes may be evident in the right ventricular outflow tract during diastole in cases of prolapsing right atrial tumor[17] or origin of the mass in the right ventricular outflow tract, as in our patient. This finding alone is of limited value in localizing the site of attachment. The systolic demonstration of a mass in the pulmonary artery, along with the presence of diastolic echoes in the right ventricular cavity, indicates that the site of attachment is in the right ventricular outflow tract.

Successful detection of right ventricular tumors requires skill in examination of the right heart chambers as well as awareness of the nature of reverberation artifacts. The latter may obscure right heart cavities or produce spurious echocardiographic patterns that require the use of varied beam positions and careful control of instrument sensitivity for correct identification.

Figure 4, which demonstrates the systolic extent of tumor excursion, contains no landmarks revealing the relation of the tumor to the pulmonary artery and valve although knowledge of the beam position and recording angle suggested that the mass did enter the pulmonary artery. The tumor echoes in this record simulated the motion pattern of an atrioventricular valve as they moved toward the transducer at the onset of diastole from a relatively stationary systolic position. Inspection of echocardiograms without knowledge of the transducer orientation could thus result in a false diagnosis of a thickened tricuspid valve or a tumor mass located in the right atrial cavity.

Differentiation from other cardiac tumors: The prominent low frequency systolic fluttering of the tumor echoes may reflect the gelatinous nature of the myxomatous mass as it undulated at the limits of its excursion, permitting quivering during the phase of most rapid blood flow (Fig. 4). This was also observed in the angiocardiogram. Additional experience is required to determine the usefulness of this finding in differen-

tiating myxomas from other cardiac tumors. The echocardiographic findings in our case are not distinctive enough to be regarded as evidence of myxoma as such and apply to other cardiac tumors as well.

Echocardiography was not useful in identifying the presence of bacterial endocarditis on the pulmonary valve because echoes from the affected cusps were not recorded.

In conclusion, an abnormal mass of echoes located in front of the pulmonary valve throughout the cardiac cycle with encroachment into the pulmonary artery in systole has been demonstrated in a patient with a right ventricular outflow myxoma prolapsing into the pulmonary artery. Abnormal diastolic echoes were also recorded in front of the aortic root and the tricuspid valve but were nonspecific because they also occur with prolapsing right atrial tumors.

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Thallium-201 Imaging With Color Display Computer System In Old Myocardial Infarction

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In 13 patients with old myocardial infarction diagnosed with use of the electrocardiogram, coronary angiogram and left ventriculogram and in 11 patients without infarction, thallium-201 imaging with a color display computer system was carried out. In the group without infarction the average ratio of activities in two regions of interest within the myocardial wall, excluding the apex, was 1.14 (1.08 to 1.23). In the group with infarction the average ratio of noninfarcted to infarcted areas was 1.44 (1.23 to 1.78). Objective detection of infarction was possible in 12 patients (92 percent) in the group with infarction. In two patients, the earlier electrocardiographic pattern of infarction had resolved by the time of imaging. These results suggest that the sensitivity of thallium-201 imaging in the diagnosis of old myocardial infarction may be greatly enhanced by objective and quantitative analysis using a color display computer system.

Electrocardiography, coronary angiography and left ventriculography have been used to diagnose acute and old myocardial infarction. In addition, myocardial imaging has recently been developed as a promising noninvasive diagnostic tool.[1] For this purpose, thallium-201 is considered superior to other radiopharmaceutical agents.[2–4]

We have sought to enhance and redefine the sensitivity of thallium-201 imaging in detecting old myocardial infarction with the addition of a color display computer system. Some objectivity and quantification were provided by comparing radioactivity in regions of interest with those in control regions in each subject.

Methods

Subjects: Thirteen patients with old myocardial infarction who were admitted to the Hospital of Kawasaki Medical School underwent myocardial imaging with thallium-201 and were selected as the infarction group. The patient's age, the age and location of the infarction and other clinical findings in seven of these patients who were also studied with coronary angiography and left ventriculography are summarized in Table I.

The diagnosis of myocardial infarction was based on the following criteria: (1) typical chest pain and serial changes in the electrocardiogram and in serum enzyme levels during the acute phase; and (2) a history of severe chest pain, an electrocardiographic pattern of old myocardial infarction and, on coronary arteriography, obstruction of the coronary artery supplying the area corresponding to the electrocardiographic abnormality. In two patients (Cases 7 and 12) the previous electrocardiographic abnormality had resolved by the time of imaging.

Eleven subjects without infarction who also had imaging constitute the control group. Two of these patients had arrhythmia, two had hypertension, five had valve disease, one had congenital heart disease and one had lung cancer.

Method: Each subject received 2 mCi of thallium-201 chloride intravenously. Five minutes later, the scintigraphy was started, using a high performance

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TABLE I

Clinical Manifestations in the Group With Old Myocardial Infarction

Case no.	Patients Age (yr)	Age of Infarct	Infarct Site (by ECG)	Coronary Angiogram (Obstruction)	Left Ventriculogram (Dyssynergy)
1	74	2 mo	Anterior	...	...
2	46	3 yr, 7 mo	Anterior	LAD	Anterior
3	43	6 mo	Anterior	LAD	Anterior
4	44	3 mo	Anterior	LAD	Anterior
5	45	3 yr	Anterior	LAD	None
6	73	2 yr, 6 mo	Anterior	...	...
7	65	45 days	Anterior	...	...
8	58	40 days	Anterior	...	...
9	47	40 days	Inferior	RCA	None
10	49	3 yr, 8 mo	Inferior	RCA	None
11	43	3 mo	Inferior	...	...
12	46	3 yr, 2 mo	Inferior	...	...
13	21	3 yr	Inferior	RCA	Inferior

ECG = electrocardiogram; LAD = left anterior descending branch; RCA = right coronary artery.

gamma camera (Nuclear Chicago Co.) connected with a color display computer system (CDP-1) (Elscint Co.).[5,6] The color images were projected on a 12 inch (30.5 cm) oscilloscope in nine colors as brown (overrange), red, orange, yellow, yellowish green, green, bluish green, blue and violet in the order of intensity of radioactivity. Imaging in each patient was completed in about 30 minutes and included views in the anterior, left anterior oblique and left lateral positions.

The images were permanently recorded on tape, and the following data were later assessed by playing back the tape:

(1) Radioactivity levels in six areas of the septum and free wall, in the apical areas and the left ventricular cavity (control group).

(2) Radioactivity levels in infarcted and noninfarcted sites (infarction group).

(3) Ratios of radioactivity levels in selected regions of interest (all subjects).

The color image data were correlated with the electrocardiogram, coronary angiogram and left ventriculogram in all patients with old myocardial infarction.

Results

Activity levels of different image sites in the control group: The average ratio of the maximal to minimal activity values of six areas in the myocardial wall, excluding the apex, in 11 control subjects was 1.14 (range 1.08 to 1.23). The average wall to apex ratio was 1.18 (1.15 to 1.28), and the average wall to left ventricular cavity ratio was 1.24 (1.12 to 1.38).

In Figure 1, the color image of a typical patient in the control group, the areas corresponding to the septal and free walls of the left ventricle are shown mainly in brown, whereas areas corresponding to the cardiac apex and the cavity are shown chiefly in red or yellow. The color images of the 10 other control patients were similar.

Activity levels in infarcted and noninfarcted sites in the infarction group: The maximal decrease in thallium-201 uptake in all eight patients with anterior myocardial infarction was in the area corresponding to the distribution of the left anterior descending artery (anterior wall), and the maximal decrease of uptake in all five patients with inferior infarction was in the area corresponding to the right coronary artery (inferior wall).

The ratio of activity levels of the noninfarcted to the infarcted areas (NIA/IA ratio) was 1.44 (1.23 to 1.78) (Fig. 2). The uptake in the infarcted area was therefore decreased 23 to 78 percent less than that in the noninfarcted area. The patients with the highest NIA/IA ratios had anterior myocardial infarction (open circles, Fig. 2).

In the two patients (Cases 7 and 12) whose earlier electrocardiographic abnormality had resolved at the

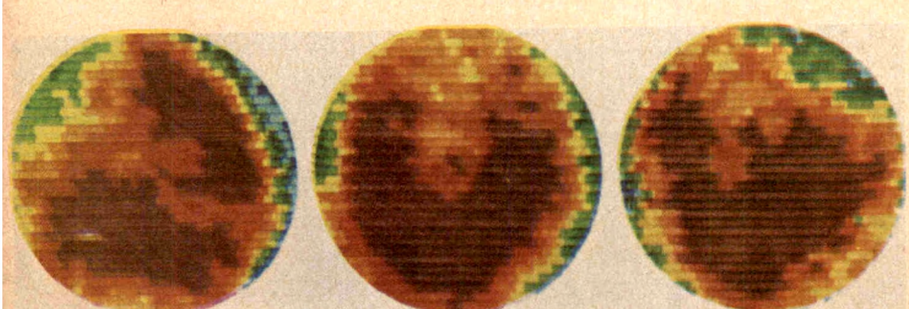


FIGURE 1. Color image from a patient in the control group. The image is mainly brown in the free and septal walls, and red or yellow in the apex and cavity of the left ventricle. A = anterior; LAO = left anterior oblique; LL = left lateral.

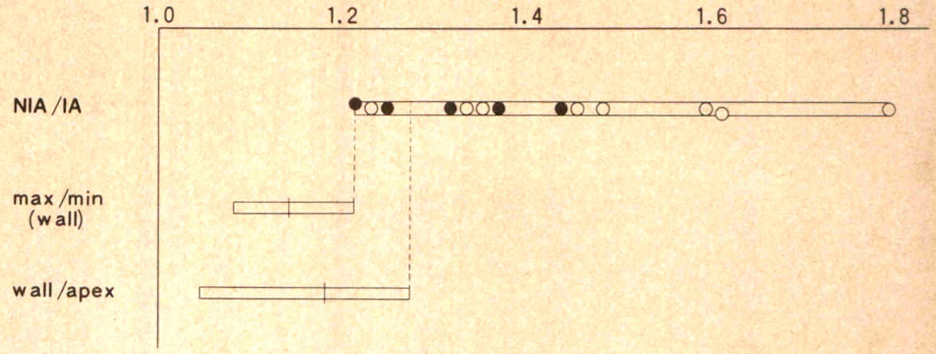


FIGURE 2. Upper horizontal bar, values of the ratios of activity in noninfarcted (NIA) versus infarcted (IA) areas in 13 patients with old anterior **(open circles)** and inferior **(closed circles)** infarction. **Middle and lower bars,** average values and the range of values in six regions of interest in the control group. Value for noninfarcted area/infarcted area ratio of one patient with inferior myocardial infarction overlapped that of the control group when the normal maximal/minimal (max/min) wall ratio was used. The values of three patients overlapped the normal value when the wall/apex ratio was used.

time of imaging, the NIA/IA ratios were clearly lower (49 percent and 33 percent, respectively) than those of the control group (8 to 23 percent).

Color image findings correlated with data from the electrocardiogram, coronary arteriogram and left ventriculogram in two patients with old myocardial infarction: *Case 3. Anterior myocardial infarction.* Figure 3 represents the electrocardiogram and arteriogram (schematic drawing) at the time of imaging in a 43 year old man who had an extensive acute anterior infarction 6 months before imaging. His electrocardiogram showed persistently abnormal Q waves, elevation of S-T segments and inverted T waves in leads I, aVL and V_1 to V_5. The coronary arteriogram revealed complete obstruction at the origin of the left anterior descending coronary artery, and the ventriculogram demonstrated dyskinesia of the anterior wall.

The color image (Fig. 4) of this patient, in contrast to those of the control group (Fig. 1), shows extensive and distinct color tone abnormalities, corresponding to the area of the left anterior descending coronary artery and anterolateral wall. The noninfarcted area/infarcted area ratio in this case was 1.59.

Case 10. Inferior myocardial infarction. Figure 5 shows the electrocardiogram and arteriogram at the time of imaging in a 49 year old man who had an acute inferior myocardial infarction 3 years and 8 months before imaging. The electrocardiogram revealed a pattern of inferior wall infarction in leads II, III and aVF, and the coronary arteriogram demonstrated complete obstruction of the right coronary artery.

The color image (Fig. 6) shows an abnormal distribution of color corresponding to the regions of the inferior wall and the right coronary artery. The noninfarcted area/infarcted area ratio was 1.39.

Discussion

Recent studies[1,4,7] have demonstrated successful identification and localization of acute transmural infarction with use of thallium-201. Studies using potassium-43 or cesium-129 have also revealed a good correlation between the site of acute infarction and electrocardiographic, coronary angiographic and left ventriculographic findings.[8,9] However, there has been no full report discussing the relative uptake levels in regions of interest in patients with old myocardial infarction as assessed with a color display computer system.

A recent study[7] suggests that thallium-201 yields some images of "negative" or "questionable" value when obtained more than 24 hours after a myocardial infarction. However, our results indicate that, with the aid of a color display computer system, old myocardial infarcts (all more than 40 days old) can be detected with a high degree of accuracy by comparing the activity levels of normal areas with those of suspected areas of infarction using the noninfarcted area/infarcted area ratio. In patients with infarction, this ratio overlapped

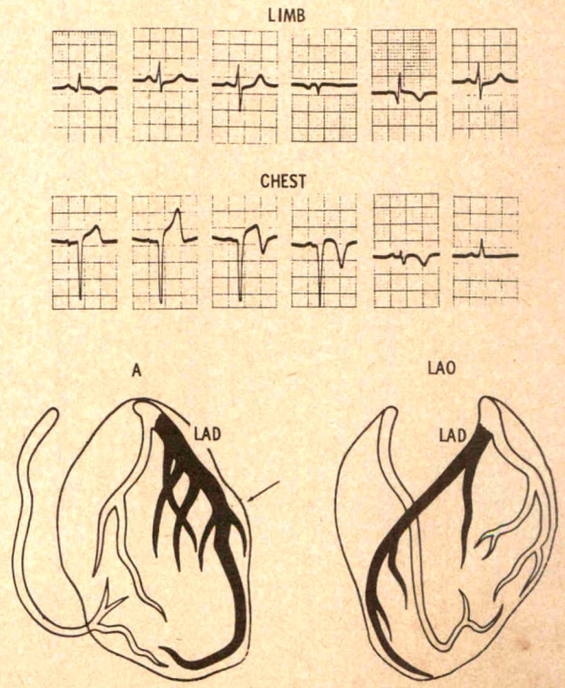


FIGURE 3. Case 3. The electrocardiogram and coronary angiogram (schematic drawing) from a patient with extensive anterior old infraction, showing complete obstruction and lack of filling of the left anterior descending artery (LAD) (drawn in black in the coronary angiogram). A dyskinetic area is indicated by the **arrow** in the left ventriculogram. A = anterior; LAO = left anterior oblique.

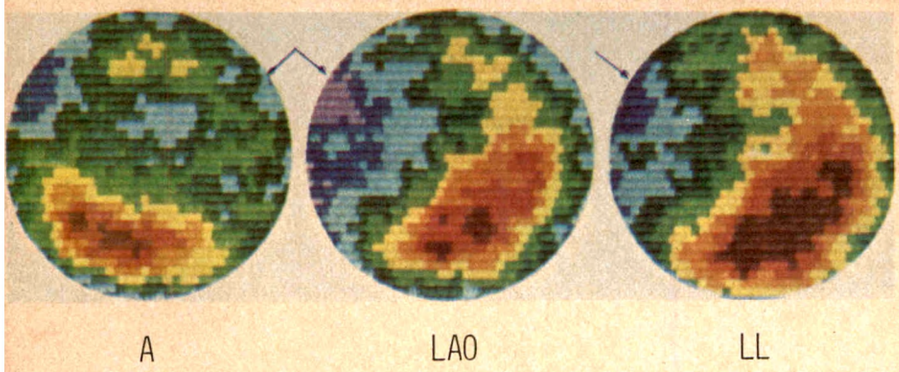


FIGURE 4. Case 3. The color image shows distinct extensive discolorations of the anterolateral wall **(arrows)** corresponding to electrocardiographic and angiographic abnormalities. Abbreviations as in Figure 1.

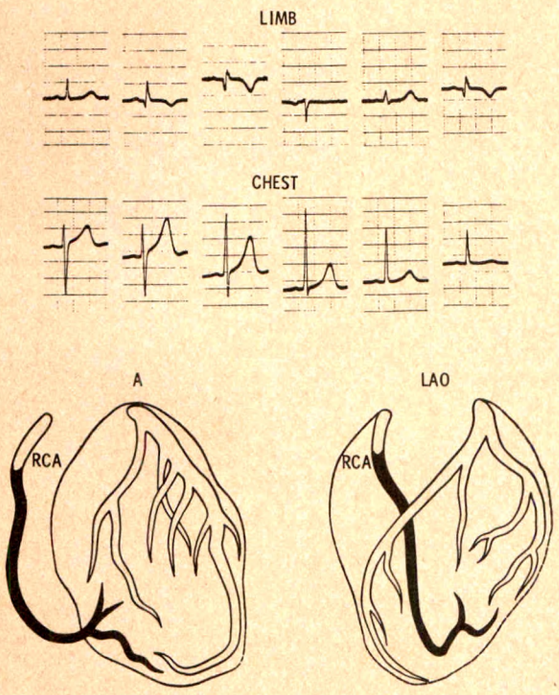


FIGURE 5. Case 10. The electrocardiogram and coronary angiogram (schematic drawing) in a patient with an old inferior infarction showing complete obstruction of the right coronary artery (RCA) (drawn in black). A = anterior; LAO = left anterior oblique.

the range of normal variation (maximal activity/minimal activity) in only 1 of 13 cases (Fig. 2). The activity levels in infarcted regions in our study ranged from 23 to 78 percent (average 44 percent) of the activity levels of normal regions. A similar range of values (29 to 68 percent) was reported by Carr[10] in dog experiments using rubidium-86.

It is important to note that when the cardiac apex area is included as a region of interest, the detection of old infarction was less specific than when this region was excluded (Fig. 2) because a wide range of thallium-201 activity was found in the apical area of normal subjects (5 to 28 percent). This normally low level of apical activity may be due to fibrous tissue in this region[11] or to the inclusion of only one wall thickness in the image of the apex compared with two walls elsewhere.

Advantages of method: Imaging with a color display computer system appears to have two main advantages over conventional monochromatic imaging with Polaroid® film: (1) The nine colors allow more exact definition of regions of reduced isotope uptake, and (2) the computer system allows more quantitative evaluation of uptake in regions of interest.

Acknowledgment

We are greatly indebted to Dr. Allan V. N. Goodyer, Professor of Internal Medicine, Yale University, for assistance in the preparation of this manuscript.

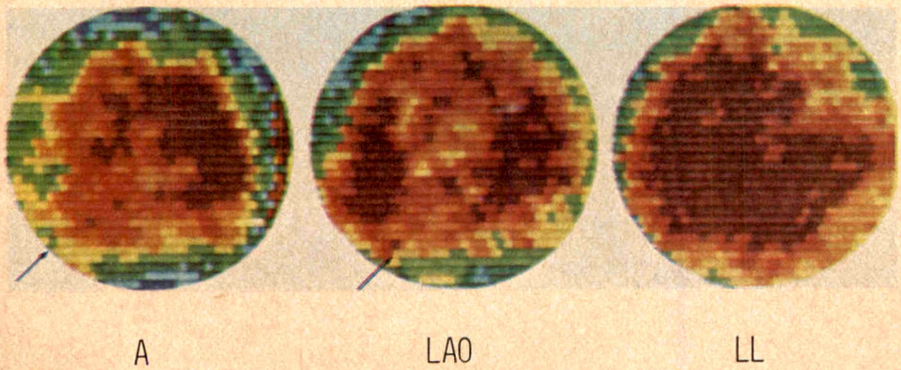


FIGURE 6. Case 10. The color image shows discoloration of the inferior wall **(arrows)** corresponding to electrocardiographic and angiographic abnormalities. Abbreviations as in Figure 1.

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Cardiac Death in Mucocutaneous Lymph Node Syndrome

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A 12 year old boy had 4 symptom-free years after hospitalization for acute febrile mucocutaneous lymph node syndrome before he died suddenly from extensive myocardial infarction. Current evidence suggests that many patients with this syndrome have coronary artery disease and that those with significant cardiac findings should be studied with coronary angiography. Serial studies are recommended because of the danger of sudden death.

Since Kawasaki[1] first described the clinical findings in acute febrile, mucocutaneous lymph node syndrome in 1967, more than 6000 cases have been reported in Japan.[2] Only recently have cases of this syndrome been reported in the United States and Canada.[3–13] Sudden death occurs in 2 percent of reported cases, generally as a result of myocardial infarction or cardiac arrhythmia and occurring in the third or fourth week of the illness.[2,14–20] Because most survivors have no symptoms of cardiovascular disease, a good prognosis is usually given to children surviving the acute illness. However, at least six deaths occurring 1 to 8 years after the onset of the illness have now been reported in Japan.[18–21] This paper describes a boy who first showed symptoms of coronary artery disease 4 years after recovering from mucocutaneous lymph node syndrome and died suddenly while awaiting scheduled coronary arterial surgery.

Case Report

An 8 year old Nisei boy was in good health until January 1972, when he presented with acute pharyngitis and was treated with orally administered clindomycin after throat cultures grew beta hemolytic streptococci. Two weeks later, he manifested fever and swelling of the right side of the neck that failed to respond to penicillin and methicillin. Because of increased fever and cervical swelling, he was admitted to a local hospital with a fever of 103°F and leukocytosis (white blood count 35,000, with 80 percent neutrophils and 9 percent stab cells). He was treated with intravenously administered penicillin and cephaloridine but continued to have a spiking fever as well as a scarlatiniform rash of the face and hands, severe hemorrhagic conjuctivitis and dry red edema of the lips. Chest and abdominal pain, mild jaundice and a mucous diarrhea were also present. Antibiotic drugs were changed to gentamycin sulfate (Garamycin®), chloramphenicol and tetracycline without response. Biopsy of an enlarged node in the neck revealed necrosis and fibrosis, and cultures were sterile. The fever persisted 14 days, and peeling of the skin of the fingertips followed. He was discharged 3 weeks after admission. During the following week he frequently complained of chest pain but did not consult his physician.

Positive laboratory studies during the illness included sedimentation rate 68 mm in 1 hour, gamma M globulin 320 mg percent, hemoglobin 8.9 g/100 ml, hematocrit 27 percent, reticulocytes 9.4 percent, bilirubin, direct 2.6 mg/100 ml, and indirect 1.1 mg/100ml. Thymol turbidity was 12 units; cephalin flocculation 3+, serum glutamic oxaloacetic transaminase 195 units, alkaline phosphatase

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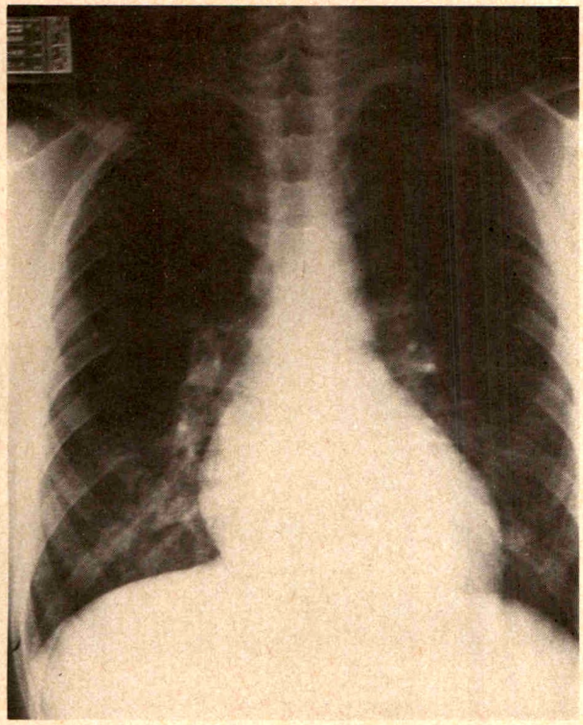


FIGURE 1. Radiograph of the chest showing mild generalized cardiac enlargement and normal pulmonary vascularity.

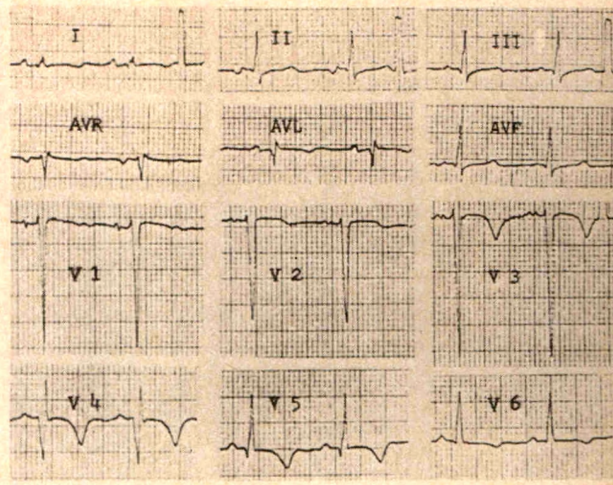


FIGURE 2. Electrocardiogram demonstrating "poor R wave progression" in the precordial leads with almost complete absence of the R wave in V_4 suggesting anterior myocardial infarction. There are diffuse nonspecific T wave abnormalities and an unusual but nondiagnostic P wave configuration in lead II.

180 mg/100 cc, prothrombin time 37 percent and antistreptolysin-O titer 333 units. Pyuria was present, but cultures were sterile. Acute and convalescent serum titers were negative for influenza A and B, adenovirus, psittacosis, Q fever, mycoplasma, typhoid H and O, paratyphoid A and B, proteus ox-19 and ox-2, brucella, Australian antigen, toxoplasmosis and leptospirosis. Skin tests were negative for tuberculosis, cat-scratch fever, coccidioidomycosis and histoplasmosis. Serial blood, urine, throat and stool cultures were negative as were heterophile, lupus erythematosus preparation, rheumatoid arthritis latex fixation and antinuclear antibody studies. During this admission, electrocardiograms and chest roentgenograms were normal.

The patient was healthy for the next 4 years except for occasional epistaxis and increased diaphoresis with exercise. In January 1976, two hours after playing soccer, he vomited and complained of chest pain. Pulse rate was 120/min. The following morning his local pediatrician obtained an electrocardiogram and referred him for cardiac evaluation. Physical examination revealed a mildly obese 12 year old Japanese boy in no distress. Blood pressure was 106/68 mm Hg. A grade II short mid-diastolic rumbling murmur was heard at the apex. There was no evidence of Marfan's syndrome, Ehler-Danlos syndrome or other connective tissue disorder. Hemoglobin was 12.5 g/100 ml, hematocrit 38.3 percent, leukocytes 8200 with normal differential.

Radiographs of the chest (Fig. 1) showed mild cardiac enlargement and normal vascularity. Echocardiogram revealed a dilated left ventricle with decreased percent fractional shortening, flat to paradoxical septal motion and decreased mitral valve velocity and excursion. The electrocardiogram demonstrated an old anteroseptal myocardial infarction (Fig. 2). Frank and cube vectorcardiograms revealed marked loss of anterior forces with initial forces to the left, typical of anteroseptal myocardial infarction. Treadmill exercise studies were attempted but were discontinued after 1 minute of jogging at 4.5 miles/hour because of short runs of ventricular tachycardia.

Right and left cardiac catheterization demonstrated a left ventricular end-diastolic pressure of 35 mm Hg increasing to 50 mm Hg after angiocardiography. Left ventricular angiograms revealed an extremely dilated left ventricle that contracted poorly. The entire anterior wall of the left ventricle was akinetic, and there was slow emptying. Left coronary angiograms revealed a 15 mm aneurysmal dilatation of the left main coronary artery immediately distal to its origin, complete occlusion of the anterior descending artery with poor collateral circulation, 95+ percent narrowing of the luminal diameter of a large diagonal artery and distal disease in the circumflex system (Fig. 3). Right coronary angiograms demonstrated complete occlusion of the right coronary artery immediately distal to the origin of a conus branch artery. Most of the distal right coronary arterial distribution was supplied by the left coronary artery through atrial and circumflex collateral vessels (Fig. 3C). The boy was scheduled for coronary bypass surgery, but was found dead in bed 1 week before the scheduled operation.

At autopsy, the heart weighed 700 g, and all chambers were dilated. The left ventricle showed marked dilatation and was red and flabby. Numerous pericardial adhesions were present. The apex of the left ventricle was thinned and contained marked fibrosis. There was severe endocardial sclerosis throughout, greatest on the ventricular septum. The heart valves were normal, and there was no evidence of congenital heart disease. The coronary orifices were normally placed. A 13 mm aneurysm containing thrombus was present in the proximal left coronary artery (Fig. 4). The left anterior descending, circumflex and right coronary arteries were thickened and the lumens narrowed. The proximal right coronary artery was totally obstructed early in its course. Careful examination of the aorta and carotid, cerebral, renal, mesenteric and iliac arteries demonstrated no evidence of vasculitis or atherosclerosis. The trachea and bronchi contained copious mucus. The lungs were heavy. There was no evidence of aspiration.

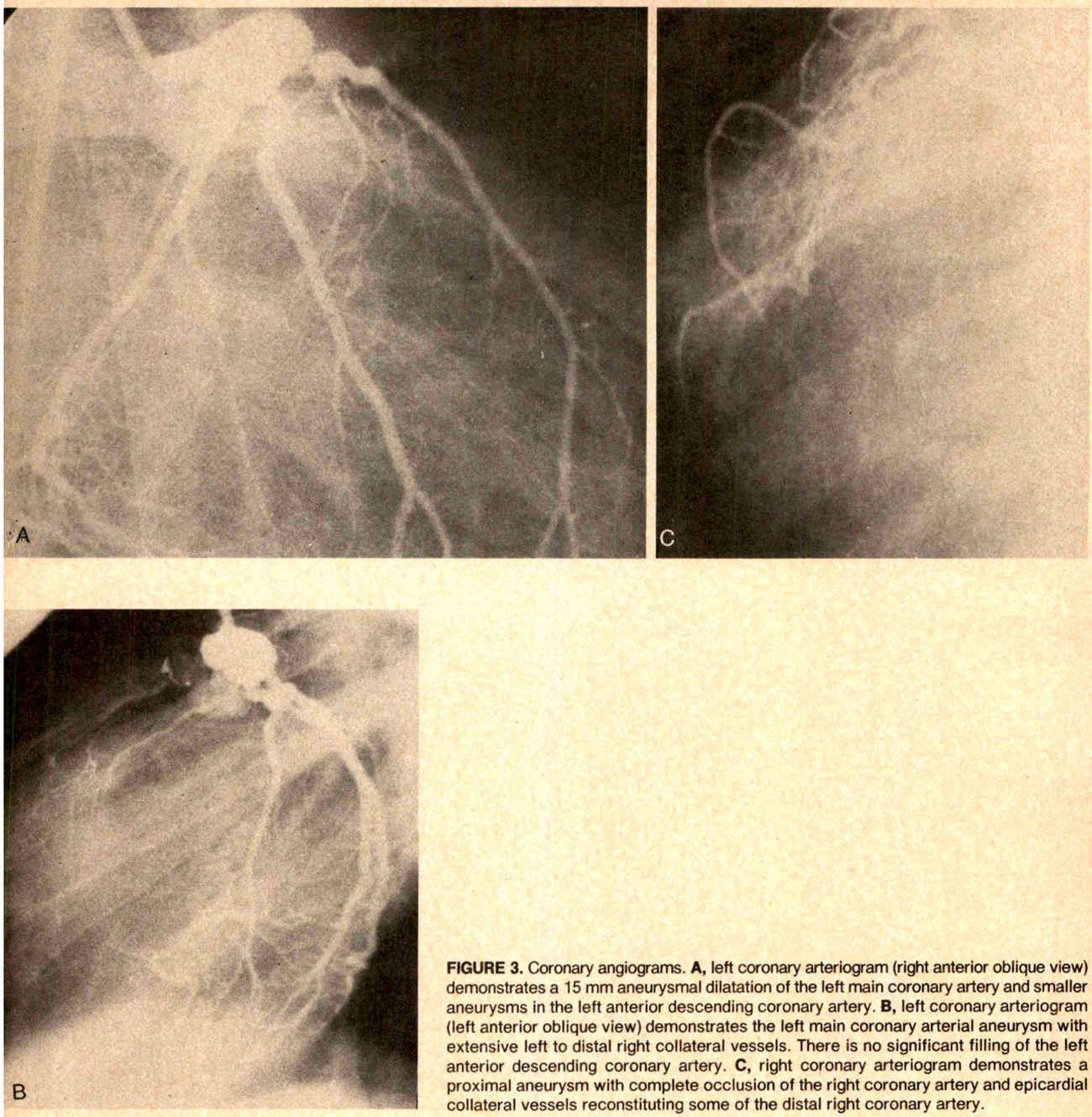


FIGURE 3. Coronary angiograms. **A,** left coronary arteriogram (right anterior oblique view) demonstrates a 15 mm aneurysmal dilatation of the left main coronary artery and smaller aneurysms in the left anterior descending coronary artery. **B,** left coronary arteriogram (left anterior oblique view) demonstrates the left main coronary arterial aneurysm with extensive left to distal right collateral vessels. There is no significant filling of the left anterior descending coronary artery. **C,** right coronary arteriogram demonstrates a proximal aneurysm with complete occlusion of the right coronary artery and epicardial collateral vessels reconstituting some of the distal right coronary artery.

Microscopic examination of the left coronary aneurysm demonstrated thickening of the media, subintimal fibrosis with marked hyalinization, and extensive calcification, and the lumen contained a recent thrombus (Fig. 4). The adjacent circumflex artery showed the same findings without calcification. The right coronary artery, 1 cm from its orifice, was completely obliterated by subintimal fibrous proliferation. Surrounding this obstructed artery were small collateral arterioles. More distal sections through all coronary arteries revealed no detectable abnormalities. All sections of myocardium showed severe nuclear hypertrophy and fibrosis. The left ventricular septum demonstrated severe endocardial sclerosis. Microscopic examination of arteries from all other organs was normal.

Review of the cervical lymph node obtained in 1972 showed obliteration of nodal architecture and severe fragmentation. The majority of cells were mature lymphocytes and frequent immunoblasts. Within the fragmented lymphoid tissue were several small foci of fibrinoid material containing nuclear debris and occasional neutrophils. No nuclear or cytoplasmic inclusions were present. The foci were smaller and less suppurative than those usually found in cat-scratch fever.

Discussion

Clinical features: Acute febrile mucocutaneous lymph node syndrome or Kawasaki's disease is a febrile illness of children occurring almost exclusively before

age 10 years and usually before age 2 years. In 1972, the Japanese Mucocutaneous Lymph Node Syndrome Research Committee formulated the following guidelines for its diagnosis[18]: (1) Fever for 5 days or more with no response to antibiotics; (2) bilateral congestion of ocular conjuctiva; (3) changes in the peripheral limbs including indurative peripheral edema and erythema of the palms and feet followed later in the illness by a membranous desquamation of the fingertips; (4) changes in the lips and mouth including dry red fissured lips, strawberry tongue and red oral and pharyngeal mucosa; and (5) a polymorphous exanthema of the trunk without crusts or vesicles. The Research Committee requires that criterion 1 and at least three of criteria 2 to 5 be met for the diagnosis to be accepted. Other frequent findings are acute nonpurulent cervical lymphadenopathy greater than 1.5 cm, mild diarrhea, arthritis or arthralgia, proteinuria and pyuria, leukocytosis with neutrophilic shift to the left, increased erythrocyte sedimentation rate and positive C-reactive protein. Evidence of aseptic meningitis, mild jaundice, increase in serum transaminase and alpha-2 globulin and evidence of carditis may also occur.

Clinically, the disease is usually misdiagnosed as scarlet fever, Stevens-Johnson syndrome, juvenile rheumatoid arthritis or infantile periarteritis nodosa. Sudden death has occurred in 1.4 to 2.5 percent of all reported cases. Cardiac causes account for 85 percent of all deaths, noncardiac causes for 6 percent and unknown causes for 9 percent.[18] The majority of deaths have occurred in the third or fourth week of the illness. Postmortem examination in fatal cases has uniformly revealed coronary arterial aneurysms with occlusion due to thromboendarteritis.[17,18] Other findings have included rupture of coronary arterial aneurysms, severe mitral insufficiency and intractable congestive heart failure due to papillary muscle dysfunction and pancarditis. The cardiac pathologic findings are identical with those previously reported in infantile periarteritis nodosa.[18,22] Review of cases of coronary arterial aneurysms in infancy reported in the United States reveals that a majority of cases were diagnosed as infantile periarteritis nodosa. In many of these cases, an initial illness identical to mucocutaneous lymph node syndrome is described.[23–27] Tanaka[22] reviewed 44 well documented cases of infantile periarteritis nodosa and found 18 cases clinically identical with mucocutaneous lymph node syndrome and 11 cases strongly suggestive of that illness. It appears likely that this syndrome has existed in the United States for many years but has been diagnosed as periarteritis nodosa, Stevens-Johnson syndrome or other illnesses.

Incidence of cardiac abnormalities: The Research Committee, supported by the Ministry of Health and Welfare of the Japanese government, reports an incidence of carditis of 4 percent.[18] However, Onouchi et al.[14] and Asai et al.[17] report electrocardiographic abnormalities or cardiac enlargement in almost all cases in the acute stage. Takao et al.[16] studied 72 cases of the syndrome from a cardiologic viewpoint and found significant electrocardiographic abnormalities in 74 percent. Retrograde aortography and coronary angiography were performed in 17 of these cases with aneurysm of the coronary arteries, narrowing, tortuosity and obstruction present in 14 (82 percent). Eight of these infants (11 percent) developed papillary muscle dysfunction with mitral insufficiency and progressive congestive heart failure. Only one infant died, death occurring during the fourth week of illness. It appears likely that the estimated 4 percent incidence rate of cardiovascular abnormalities is too low.

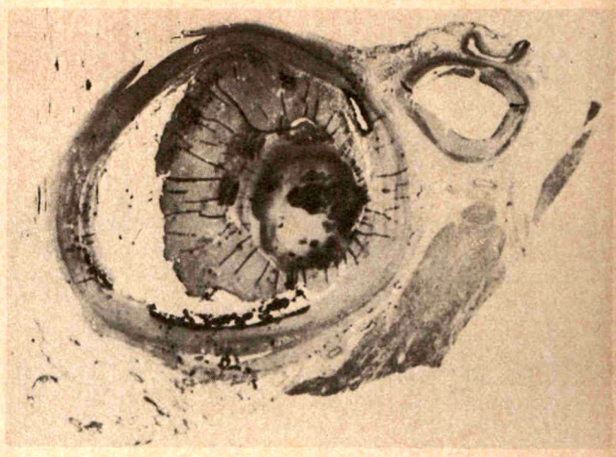


FIGURE 4. Section through the left coronary aneurysm and widened circumflex artery shows attenuation and hyalinization of muscular layers. Fragmentation and duplication of external and internal elastic lamellae were demonstrated with elastic stain. More than 50 percent of the wall thickness is composed of hyalinized fibrous tissue internal to the internal elastic lamellae. Calcium deposits are numerous and limited to the hyalinized tissue. The aneurysm contains attached and organizing thrombus (hematoxylin-eosin × 5, reduced by 28 percent).

Prognosis: Most reports have suggested an excellent prognosis in children surviving the acute phase of the illness. However, Kato et al.,[15] studying serial coronary angiograms in four patients, found regression of the coronary arterial lesions in only two, and evidence of significant coronary artery disease as late as 2 years after the onset of the syndrome in the others. Several cases of late death from coronary artery disease and extensive myocardial infarction 1 to 8 years after the onset of the illness have been reported.[20,22,23] Kitamura et al.[28] described a 4 year old boy who had a myocardial infarction 10 months after the acute illness and underwent aortocoronary bypass grafting 5 months later. Theirs is the only reported case of bypass surgery.* Our patient was awaiting scheduled bypass surgery when he died of severe coronary arterial lesions 4 years after the acute illness.

The etiology of the mucocutaneous lymph node syndrome is not established.[29] Rickettsia-like bodies in patients with this syndrome have been observed in Japan[30] and England.[31] Some authors[18,20] have suggested an autoimmune response similar to periarteritis

* Editor's note: Except for the cases reported in this issue of the Journal by Kitamura et al. (p. 156–164)

nodosa. Other causes such as abnormal host reaction to a variety of infections and allergic reaction to chemical detergents have also been postulated.[2,31]

Therapeutic implications: Although 98 percent of infants with the mucocutaneous lymph node syndrome survive, the state of the coronary arteries in the majority of these children is not known. Late coronary arterial death in patients without obvious cardiac involvement does occur, and the long-term prognosis of children recovering from the acute illness is not known. It is imperative that all children with this syndrome have extensive cardiac evaluation during the acute illness, including serial electrocardiograms, enzyme studies, chest X-ray films and echocardiograms. It is not known if antimyocardial antibody studies would be helpful in this disease, but evaluation of this new study appears warranted.[32] We consider that coronary angiography is indicated in all children with evidence of significant cardiac involvement. All patients with proved coronary artery aneurysm or obstruction should have serial studies. Until more evidence is available, a guarded prognosis should be given to any child with coronary arterial abnormalities after the mucocutaneous lymph node syndrome. If surgery is indicated, it should be expeditiously accomplished because of the danger of sudden death as demonstrated in our case.

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Isolated Coronary Periarteritis: Report of a Case of Unexpected Death in a Young Pregnant Woman

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A case of sudden unexpected death in a 23 year old woman in her 8th month of pregnancy is reported. Death occurred from isolated coronary periarteritis with thrombosis. It is believed that the thrombosis was secondary to the adventitial infiltrate, which was of a type suggesting a hypersensitivity factor. It is proposed that pathogenetically this case is identical to reported cases of dissecting hemorrhage or aneurysm of the coronary artery and represents an entity different from other forms of inflammatory coronary disease.

This is the case of a young woman in the 8th month of pregnancy who died unexpectedly from isolated thrombosing coronary periarteritis.

Case Report

The patient was a 23 year old white primipara in the 8th month of an essentially uneventful pregnancy. The date of expected delivery was November 28, 1974. She had received the usual prepartum care. Her previous medical history was normal. There was no family history of cardiovascular disease but one sister had bronchial asthma. Her weight was 113.4 kg when she was first seen by her physician in May 1974 but had decreased to 90 kg by September. Her blood pressure increased from 120/80 to 140/70 mm Hg during the same period. A blood count in June was normal with 1 percent eosinophils.

The patient arrived at the emergency room of W. A. Foote Memorial Hospital, Jackson, Michigan, at 8:35 PM on October 5, 1974, complaining of nausea and retrosternal pain. Her temperature was 98.6 F, blood pressure 160/80 mm Hg and pulse rate 100/min. Blood count revealed a mild anemia with 1 percent eosinophils. An electrocardiogram showed no diagnostic changes. She was given an antacid and Valium®, 10 mg, and sent home at 10:20 PM. At 11:50 PM, when she returned with the same complaints, she was given Demerol®, 75 mg, and again sent home with the diagnosis of anxiety. At 5:45 the next morning she was dead on arrival at the hospital. The man with whom she lived stated that she woke up screaming, then fell back in bed and remained unresponsive. When the ambulance arrived, her pupils were dilated and fixed and resuscitation attempts were unsuccessful.

Autopsy findings: There was evidence of resuscitation trauma on the anterior chest wall. The heart weighed 385 g. In the left anterior descending coronary artery, close to its origin, there was an apparent postmortem clot. The myocardium and aorta appeared normal. In the uterus there was a normally developed male fetus measuring 47 cm in length. The rest of the organs appeared normal. No cause of death was established on gross examination.

On microscopic examination, the clot in the left anterior descending coronary artery was found to be a mixed thrombus occluding the lumen (Fig. 1). The intima and subintimal stroma were moderately thickened and the stroma showed localized edema. A few lipophages were seen under the endothelial lining. In one place, the thrombus was loosely attached to the intima and a small infiltrate of neutrophils was found superficially invading the intima. The muscular coat was normal. The adventitia showed moderate fibrous thickening and was densely infiltrated with cells that formed a cuff around the artery (Fig. 1) and consisted of neutrophils, eosinophils, lymphocytes and occasional histiocytes (Fig. 2). Verhoeff's elastic stain revealed some flattening of the internal elastic membrane. A Van Gieson stain confirmed the increase in fibrous tissue in the subintimal

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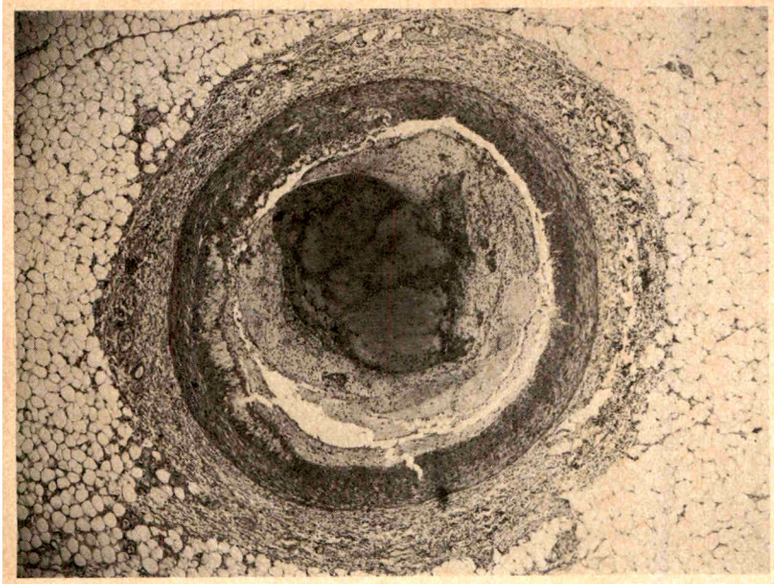


FIGURE 1. Occlusion of coronary artery by thrombus. Subintimal edema and a perivascular infiltrate are present. (Hematoxylin-eosin ×40, reduced by 10 percent.)

stroma and adventitia. A mucicarmine stain was noncontributory. No changes were evident in the myocardium, intramural coronary branches or thoracic aorta.

The diagnosis was acute thrombosis and periarteritis of the left anterior descending coronary artery causing sudden death in a young pregnant woman.

Review of Literature

Nonatherosclerotic coronary occlusion is rare in the clinical and pathologic material of the average community hospital. When it does occur, it is likely to come under the jurisdiction of the medical examiner, as it did in this case, and is therefore of particular interest to the forensic pathologist. In view of the suddenness of death, the majority of these cases have not been investigated clinically, depriving the clinician of valuable information and permitting only limited scientific study.

There are numerous types of nonatherosclerotic coronary disease. Cheitlin et al.[1] present a long list of mostly unusual pathologic entities including specific and nonspecific coronary arteritis, trauma, metabolic disease, embolism, congenital anomalies and many others. Some cases are morphologically indistinguishable from atherosclerosis. Vasicka and Lin[2] reported the case of a 21 year old woman who died post partum from intimal thickening of a coronary artery causing almost complete occlusion. Young et al.[3] reported a similar nonfatal case of an 18 year old girl who had severe angina pectoris; coronary stenosis was demonstrated at cardiac catheterization and angiography, and she was successfully treated with bypass surgery. Coronary disease due to tuberculosis is occasionally found in parts of the world where the latter disease is still common.[4] Lupus erythematosus involving the coronary arteries was reported by Bonfiglio et al.[5] Takayasu's disease, which focally involves the aorta, may extend into the coronary arteries where it presents as an inflammatory and degenerative process that gradually affects all layers of the coronary wall.[6–8] A fairly new disease entity, first described by Kawa-

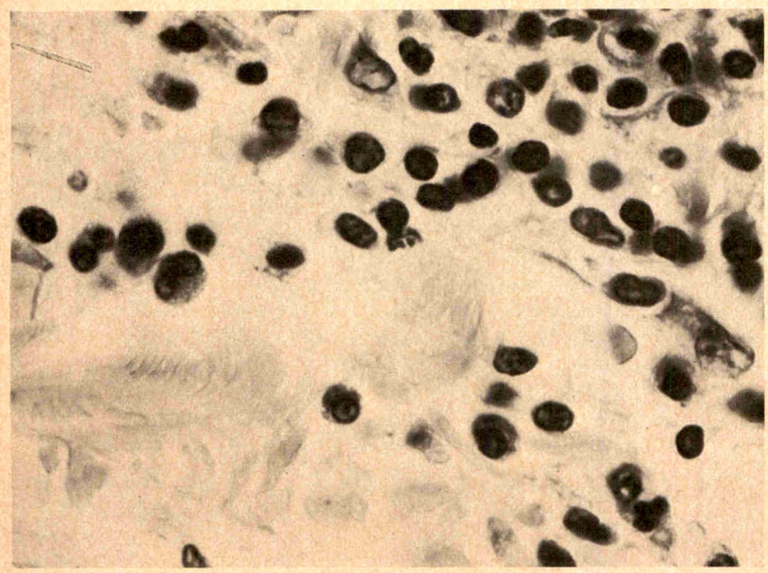


FIGURE 2. Perivascular infiltrate consisting of neutrophils, eosinophils, lymphocytes and histiocytes. (Hematoxylin-eosin, oil immersion ×1000, reduced by 10 percent.)

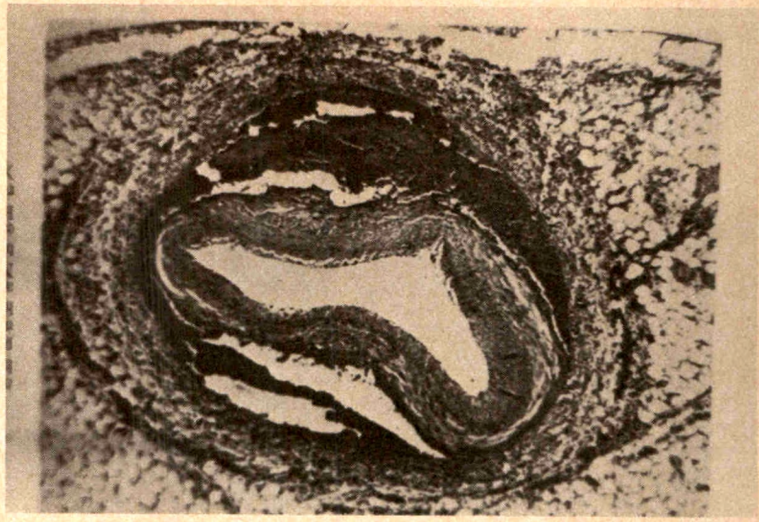


FIGURE 3. Dissecting hemorrhage in wall of coronary artery in a previously reported case[18] showing striking similarity of the perivascular infiltrate with that shown in Figure 1. (×35, reduced by 20 percent.) (Reproduced with permission of the editor of the *Archives of Pathology*.[18])

saki[9] in 1967, is acute febrile mucocutaneous lymph node syndrome. It is found in infancy and early childhood and closely resembles infantile periarteritis nodosa. Fatal cases uniformly show occlusion of the coronary arteries and, in some instances, coronary aneurysms.[10,11]

Immunologic factors may be the underlying cause of coronary disease in some of the collagen diseases. In rheumatoid arteritis the disease may become manifest in the intramural branches of the coronary arteries, which are narrowed and show signs of healed angiitis, although the extramural branches may be normal.[11] Zeek,[13] in her classification of necrotizing angiitis, lists allergic granulomatous, rheumatic and hypersensitivity angiitis commonly affecting the heart. Saphir et al.[14] found changes suggesting old periarteritis in the intramural branches of the coronary arteries in 32 of 82 cases and a history of hypersensitivity in 12 of 100 cases of coronary atherosclerosis. Immunologic factors having a bearing on inflammatory coronary disease are suggested by several experimental studies.[15–17]

Discussion

The principal feature of this case was the unexpected death from coronary thrombosis of nonatherosclerotic origin of a young woman in the last trimester of pregnancy. The main pathologic changes were in the adventitia, which showed an inflammatory infiltrate of a type suggesting a hypersensitivity factor. The finding was isolated and found in no other part of the body or any other level of the coronary system. The localized involvement and the lack of changes in the muscular coat distinguish this case from other cases of nonatherosclerotic coronary disease. In 1959 Wagman and I reported the sudden death of a 41 year old woman from what we called "dissecting hemorrhage in the media of the coronary artery." The artery manifested the identical inflammatory infiltration in the adventitia found in the present case. In retrospect and in the light of the present findings, I now consider that both cases represent the same entity. The striking similarity of the adventitial changes in the two cases is shown in Figures 1 and 3. If this interpretation is correct, one may assume that the adventitial infiltrate is the primary pathologic finding and the intramural hemorrhage and the thrombosis in the respective cases are secondary. It then appears justified to identify as the same entity previously reported cases diagnosed as dissecting hemorrhages or hematomas in coronary arteries[19–22] or, perhaps not quite correctly in the strict sense of the term, as aneurysms.[23,24] All these cases are isolated and uniformly show the identical adventitial infiltrate of neutrophils, eosinophils, lymphocytes and histiocytes.

A relation probably exists between the pregnancy and the fatal disease in this case. Katz[25] found only one case of "Herzmuskelmalazie," presumably myocardial infarct, in 95 cases of sudden death during pregnancy and puerperium. More recently, several such cases have been reported in pregnant and postpartum women. Asuncion and Hyun[22] added 3 cases to 7 reported since 1952; of these 10 cases, 2 occurred during the 9th month of pregnancy, 7 during the immediate postpartum period and only 1 as late as 80 days post partum.

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Appraisal of Treatment for Left Main Coronary Artery Disease

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The left main coronary artery supplies blood to a large portion of the left ventricle. Significant obstruction in this vessel may jeopardize substantial areas of the myocardium, with such potential serious consequences as infarction, arrhythmias, cardiogenic shock and congestive failure. Fortunately, left main coronary artery disease has a small incidence rate; it affects only about 5 percent of patients with coronary artery disease.[1–4] Moreover, 95 percent or more of the patients with left main coronary artery disease also have disease of one or more of the three other major coronary arteries. In our experience, as well as that of others, patients with disease of the left main coronary artery cannot be separated on the basis of clinical, electrocardiographic, hemodynamic or ventriculographic criteria from patients whose coronary disease does not involve this artery.[1–7]

At present, coronary arteriography is the only reliable method for positively identifying patients with left main coronary artery disease. Early reports[3,7,8] suggested that in this group there is increased mortality associated with coronary arteriography. However, recent studies have shown that arteriography can be carried out with an acceptable risk, presumably because of increased awareness and the special care taken in accordance with the recommendations of many investigators.[5,9–11] Such care includes use of techniques such as flush injection of the left coronary sinus of Valsalva; if narrowing of the left main coronary artery is seen, cardiac catheterization should be carried out expeditiously and the injections kept to the minimum required for adequate visualization of the coronary vessels. The tip of the catheter should be positioned cautiously, and it should be withdrawn between injections whenever monitoring with the catheter tip reveals damping of the systemic pressure. This precaution is crucial when there is also significant narrowing of the right coronary artery, a common finding in these patients. Nitroglycerin should be used whenever angina pectoris develops. It is our policy to monitor patients with left main coronary artery disease in the coronary care unit for 24 hours after cardiac catheterization, with the surgical team standing by in case emergency revascularization is needed.

With use of these guidelines we have had no morbidity or mortality among 130 patients with left main coronary artery disease studied since February 1972. It is probably correct that the minimal risk (0.2 percent mortality rate) associated with coronary arteriography in many laboratories performing a large number of procedures can be ascribed to patients with left main coronary artery disease, and unstable angina pectoris.[12]

In establishing the prognosis and treatment of patients with left main coronary artery disease, two determinations must be made: (1) the status of left ventricular function, as assessed with left ventriculography, and (2) the status of the distal coronary arteries. A poor left ventricular contraction pattern, as seen with left ventriculography, is usually manifested by diffuse, significant hypokinesia and an injection fraction of 30 percent or less.[13,14] The left ventricular end-diastolic pressure in these patients is frequently elevated, as are the pressures in the left atrium and right heart chambers. Some patients may have the symptoms and signs of congestive heart failure.

The diameter of the vessel beyond the proximal obstruction and the area of distribution, as well as the presence or absence of distal atherosclerosis, are important factors in assessing the long-term patency of saphenous vein bypass grafts.[15] However, angiographic determination of the distal runoff is least reliable in the presence of total obstruction with retrograde filling of the distal vessels.[16] It is therefore not surprising to find at operation a vessel with normal caliber although prior coronary angiography had only faintly visualized an apparently small distal vessel.

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What Is Proper Management?

The results of aortocoronary bypass surgery in patients with left main coronary artery disease and reasonably good left ventricular function show that symptoms can be dramatically decreased at an acceptable surgical risk.[2,17] The surgical mortality at our institution, as in others,[17,18] has been slightly greater in patients with left main coronary artery disease than in the total group undergoing coronary arterial bypass surgery. The decrease in such mortality over the past 3 years in patients with left main coronary artery disease can be attributed in significant measure to improved surgical technique and greater emphasis on completeness of revascularization; improved perioperative patient management has also played an important part. The increasing awareness of the necessity to control myocardial ischemia immediately before, during and after operation has unquestionably reduced the incidence of perioperative myocardial infarction and has lessened surgical mortality.

Decreasing the ventricular afterload with intravenously administered nitroprusside or nitroglycerin, with a consequent reduction in the demand for myocardial oxygen, has been extremely effective in preventing ischemia during induction of anesthesia and in the early period after the bypass procedure. Not surprisingly, many episodes of hypotension and progressive myocardial infarction during bypass surgery for lesions of the left main coronary artery were preceded by myocardial ischemia associated with relative hypertension or an increase in the heart rate-pressure product. Careful avoidance of even transient episodes predisposing to myocardial ischemia has greatly decreased the incidence of serious hypotension and arrhythmias.

Another factor contributing to improved stability in the condition of patients with left main coronary artery disease and marginal myocardial perfusion during bypass surgery is the use of propranolol therapy throughout the immediate preoperative period, particularly during cardiac catheterization and coronary arteriography. Physicians are becoming increasingly aware of the problems of progressive myocardial ischemia upon abrupt withdrawal or even gradual tapering off of propranolol preoperatively. Thus, careful pharmacologic management of such patients has to some extent diminished the urgency of bypass surgery. Unquestionably, emergency bypass surgery in the presence of acute myocardial ischemia is associated with increased operative mortality and morbidity resulting from perioperative myocardial infarction.

On occasion, there may be repeated episodes of myocardial ischemia despite careful medical management. In this circumstance, the use of circulatory assistance in the form of intraaortic balloon pumping has proved extremely effective in resolving ischemia and stabilizing the condition of patients with left main coronary artery disease in preparation for urgent coronary bypass surgery.[19] Even in the presence of unstable and medically refractory ischemia, intraaortic balloon pumping has reduced operative mortality and the rate of perioperative myocardial infarction to levels comparable with those associated with elective bypass surgery for stable coronary artery disease.[20]

Several recent studies[2,9,17,20–22] have also shown that patients with left main coronary artery disease who undergo bypass operations live longer than comparable patients treated medically. McConahay et al.,[17] for example, found that the mortality rate, including surgical mortality, in the first postoperative year was 3.8 percent, with a 3.3 percent annual mortality rate in an average follow-up period of 18.1 months. This compares favorably with the annual mortality rate of 15 to 35 percent reported for patients with left main coronary artery disease managed medically over a similar period.[1,6,7]

The outlook for patients with left main coronary artery disease and poor left ventricular function is poor indeed with either medical therapy or surgery.[1,3,6] Surgery no doubt carries a higher risk; whether it improves survival in this group of patients remains to be seen. Urschel and Razzuk[13] reported a reduction in operative mortality and morbitity in patients with poor left ventricular function and left main coronary artery disease after instituting certain modifications in intraoperative management. Avoidance of significant hypotension during induction of anesthesia was accomplished by means of femoral to femoral partial cardiopulmonary bypass in 6 of 24 patients in whom hypotension and progressive myocardial ischemia (or both) developed. Right coronary artery disease was present in all 24 patients; a vein bypass graft was performed to this vessel immediately in all 24, with a high proximal aortic anastomosis being used to minimize subsequent myocardial ischemia by allowing cross-clamping below the origin of the graft to the right coronary artery. There were no operative deaths in this group.

In patients with severe lesions of the left main coronary artery whose distal left anterior descending and left circumflex arteries are seen but are poorly visualized because of ineffective collateral vessels, it may still be advisable for the surgeon to attempt to locate vessels that can be bypassed. In patients with angiographic evidence of severe atherosclerosis involving both the distal left anterior descending and left circumflex arteries in association with left main coronary artery disease, surgery is ill advised.

Patients with left main coronary artery disease can undergo coronary arteriography and coronary bypass surgery at a low level of acceptable risk. Current data suggest that in these patients coronary bypass surgery may be preferable to medical treatment because of the better survival rate and greater relief of symptoms. Although we do not advocate randomization for this lesion, the ongoing randomized prospective studies of large numbers of patients, such as that reported by Takaro et al.[22] from the Veterans Administration Cooperative Group, may serve to establish definitively the comparative long-term merits of medical and surgical treatment in patients with left main coronary artery disease.

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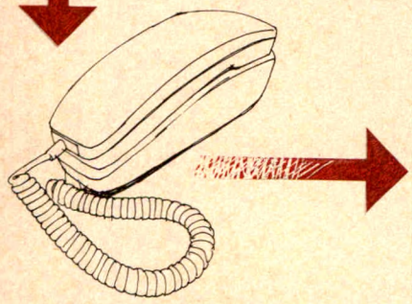
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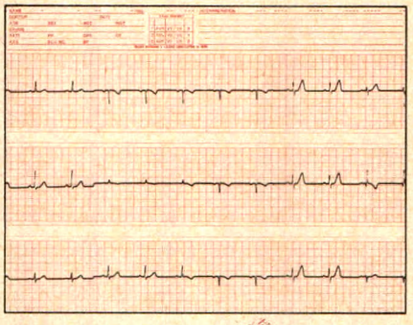
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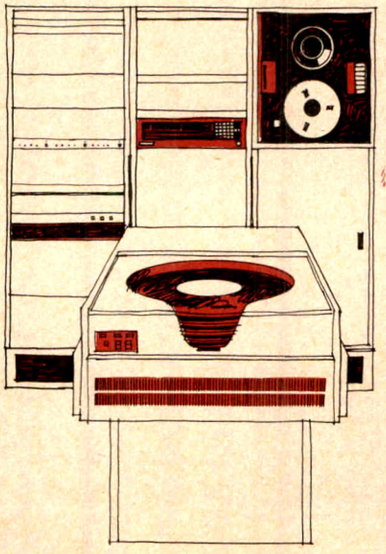
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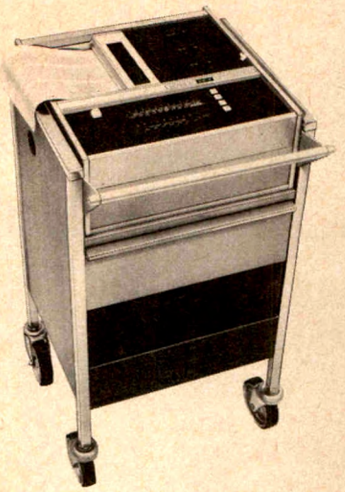
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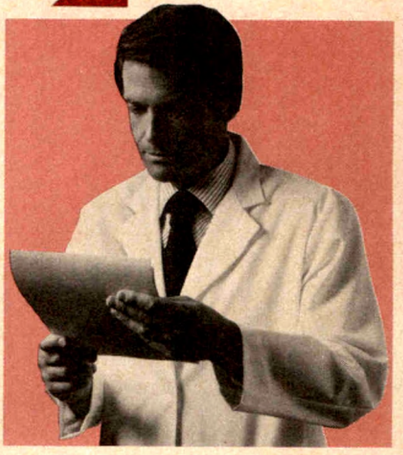
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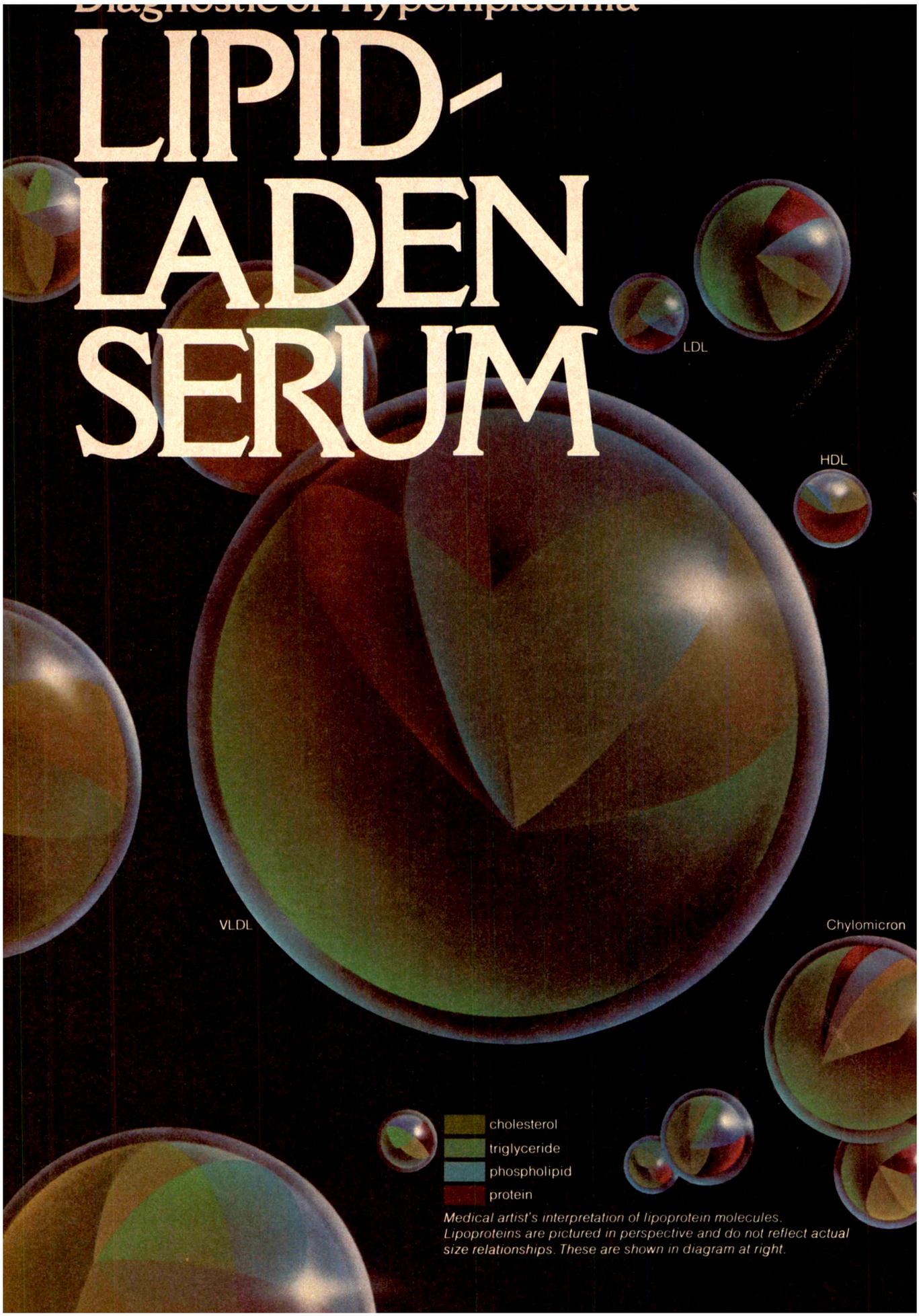
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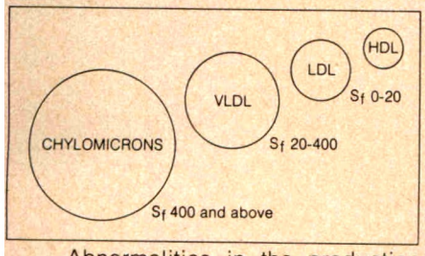


Medical artist's interpretation of lipoprotein molecules. Lipoproteins are pictured in perspective and do not reflect actual size relationships. These are shown in diagram at right.

Lipoproteins: The "cargo" and the "transport vehicle"

Since fats are insoluble in water, they must link up with protein to remain dispersed in the blood. The lipoprotein molecules thus formed allow lipid substances—cholesterol, triglycerides, phospholipids—to travel freely in a soluble form through the bloodstream for use as structural building blocks and sources of energy. The four major classes of lipoprotein, consisting of varying amounts of lipids (the "cargo") and protein (the "transport vehicle") are chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). [See medical artist's interpretation at left.] The relative size of these lipoprotein molecules, based on measurement of flotation rates via ultracentrifugation, is shown below.

SCHEMATIC RELATION OF SIZE TO FLOTATION RATE (S_f)



Abnormalities in the production and/or degradation of these lipoproteins can lead to excessive accumulations of cholesterol and/or triglycerides in the serum. These elevations in serum lipids, in the absence of underlying causative disease, are diagnostic of hyperlipidemia.

Early intervention—a rational approach to the management of hyperlipidemia

Reducing elevated lipid levels is a rational therapeutic goal at any point in the hyperlipidemic process—but is perhaps most logical in the early stage. This is the stage when most patients are asymptomatic, yet routine cholesterol and triglyceride determinations will disclose that nevertheless they are hyperlipidemic.[1]

If persistent, clinically significant lipid elevations are demonstrated—and underlying disease states are ruled out through history, physical examination, and appropriate laboratory tests—a diagnosis of primary hyperlipidemia is confirmed.

Dietary modification directed at correcting the specific lipid abnormality should be instituted as the first therapeutic step, but it often fails to lower the lipids sufficiently.

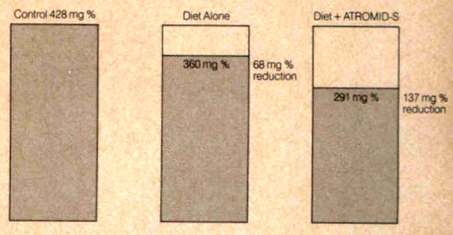
This is the best time to add ATROMID-S, an antilipidemic agent, to the regimen. Early, effective, and continuous lipid lowering is important in the successful management of hyperlipidemia.

When diet alone is not enough, Atromid-S can further reduce elevated serum lipids

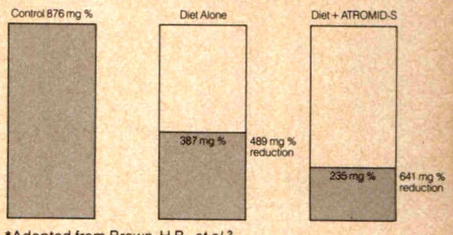
As an adjunct to diet and other measures, ATROMID-S depresses levels of both the very low density lipoproteins (S_f 20-400) and the low density lipoproteins (S_f 0-20), with an apparently greater effect on the former. The result of these actions is a reduction in elevated serum cholesterol (particularly the cholesterol carried by LDL) and/or triglycerides.

AN IMPORTANT NOTE: It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

ATROMID-S Lowers Cholesterol Significantly Better Than Diet Alone
Results in 7 patients with hypercholesterolemia
Mean Difference mg %*



ATROMIDS-S Lowers Triglycerides Significantly Better Than Diet Alone
Results in 7 patients with hypertriglyceridemia
Mean Difference mg %*



*Adapted from Brown, H.B., *et al.*[2]

Continuous therapy and constant dosage essential to long-term control

Lipid lowering is sustained as long as ATROMID-S treatment is uninterrupted. However, if the drug is stopped, lipid levels may return to or above pretreatment levels.

ATROMID-S is effective in a simple, well-accepted regimen. Initial *and* maintenance dosage is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

IF GIVEN IN CONJUNCTION WITH ANTICOAGULANTS

WARNING: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

As an adjunct to diet

Atromid-S®

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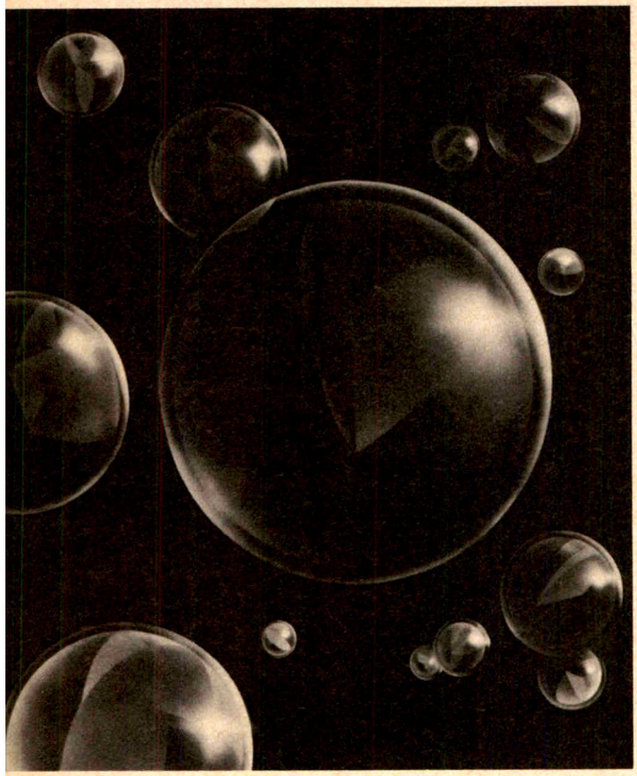
clofibrate

Helps reduce elevated serum levels of cholesterol and/or triglycerides

See last page of this advertisement for prescribing information.

Atromid-S® (clofibrate)

Helps reduce elevated serum levels of cholesterol and/or triglycerides



BRIEF SUMMARY
(For full prescribing information, see package circular.)

ATROMID-S® Brand of clofibrate

Antilipidemic agent for reduction of elevated serum lipids

INDICATIONS: ATROMID-S is indicated as adjunctive therapy to diet and other measures for the reduction of elevated serum cholesterol (especially the beta lipoprotein fraction) and/or triglycerides. Clofibrate appears to have a greater depressant effect on the very low density lipoproteins (S_f 20-400) rich in triglycerides than the low density lipoproteins (S_f 0-20) rich in cholesterol.

ATROMID-S is also indicated for treatment of patients with xanthoma tuberosum associated with hyperlipidemia. The skin lesions frequently regress with clofibrate.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUALLY BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Strict birth control procedures must be exercised by women of childbearing potential. In patients who plan to become pregnant, clofibrate should be withdrawn several months before conception. Because of the possibility of pregnancy occurring despite birth control precautions in patients taking clofibrate, the possible benefits of the drug to the patient must be weighed against possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to control serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diabetes mellitus, etc.

Because of the long term administration of a drug of this nature, adequate base line studies should be performed to determine that the patient has significantly elevated serum lipid levels. Frequent determinations of serum lipids should be obtained during the first few months of ATROMID-S administration, and periodic determinations thereafter. The drug should be withdrawn after three months if response is inadequate. However, in the case of xanthoma tuberosum, the drug should be employed for longer periods (even up to one year) provided that there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in serum cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cholesterol peak elevations in midwinter and late summer and decreases in fall and spring. If the drug is discontinued, the patient should be placed on an appropriate hypolipidemic diet, and his serum lipids should be monitored until stabilized, as a rise in these values to or above the original base line may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver function tests should be performed since the drug may produce abnormalities in these parameters. These effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually within normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the drug should be withdrawn. Therefore use with caution in those patients with a past history of jaundice or hepatic disease.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The physician should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether this is drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more frequently, leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decrease in cholesterol linoleate but an increase in palmitoleate and oleate, the latter being considered atherogenic in experimental animals. The significance of this finding is unknown at this time.

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less frequently encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, and abdominal distress. Reactions reported less often than gastrointestinal ones are headache, dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, and pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular
- Increased or decreased angina
- Cardiac arrhythmias
- Both swelling and phlebitis at site of xanthomas

Dermatologic
- Skin rash
- Alopecia
- Allergic reaction including urticaria
- Dry skin and dry brittle hair
- Pruritus

Gastrointestinal
- Nausea
- Diarrhea
- Gastrointestinal upset (bloating, flatulence, abdominal distress)
- Hepatomegaly (not associated with hepatotoxicity)
- Gallstones
- Vomiting
- Stomatitis and gastritis

Genitourinary
- Impotence and decreased libido
- Findings consistent with renal dysfunction as evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal biopsy suggested "allergic reaction."

Hematologic
- Leukopenia
- Potentiation of anticoagulant effect
- Anemia
- Eosinophilia

Musculoskeletal
- Myalgia (muscle cramping, aching, weakness)
- "Flu like" symptoms
- Arthralgia

Neurologic
- Fatigue, weakness, drowsiness
- Dizziness
- Headache

Miscellaneous
- Weight gain
- Polyphagia

Laboratory Findings
- Abnormal liver function tests as evidenced by increased transaminase (SGOT and SGPT), BSP retention, and increased thymol turbidity
- Proteinuria
- Increased creatine phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been established: peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspiration, systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g daily, in divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conjunction with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one-half (depending on the individual case) to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdosage, should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: ATROMID-S—No. 243—Each capsule contains 500 mg clofibrate, in bottles of 100.

References: 1. Scheig, R.: Conn. Med. *39*:71 (Feb.) 1975. **2.** Brown, H. B., Lewis, L. A., and Page, I. H.: Clin. Pharmacol. Ther. *17*:171 (Feb.) 1975.

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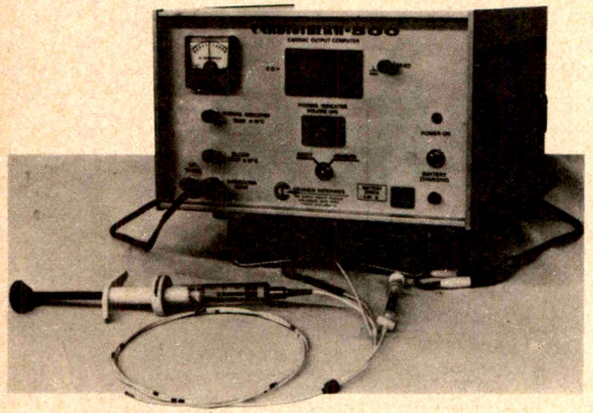


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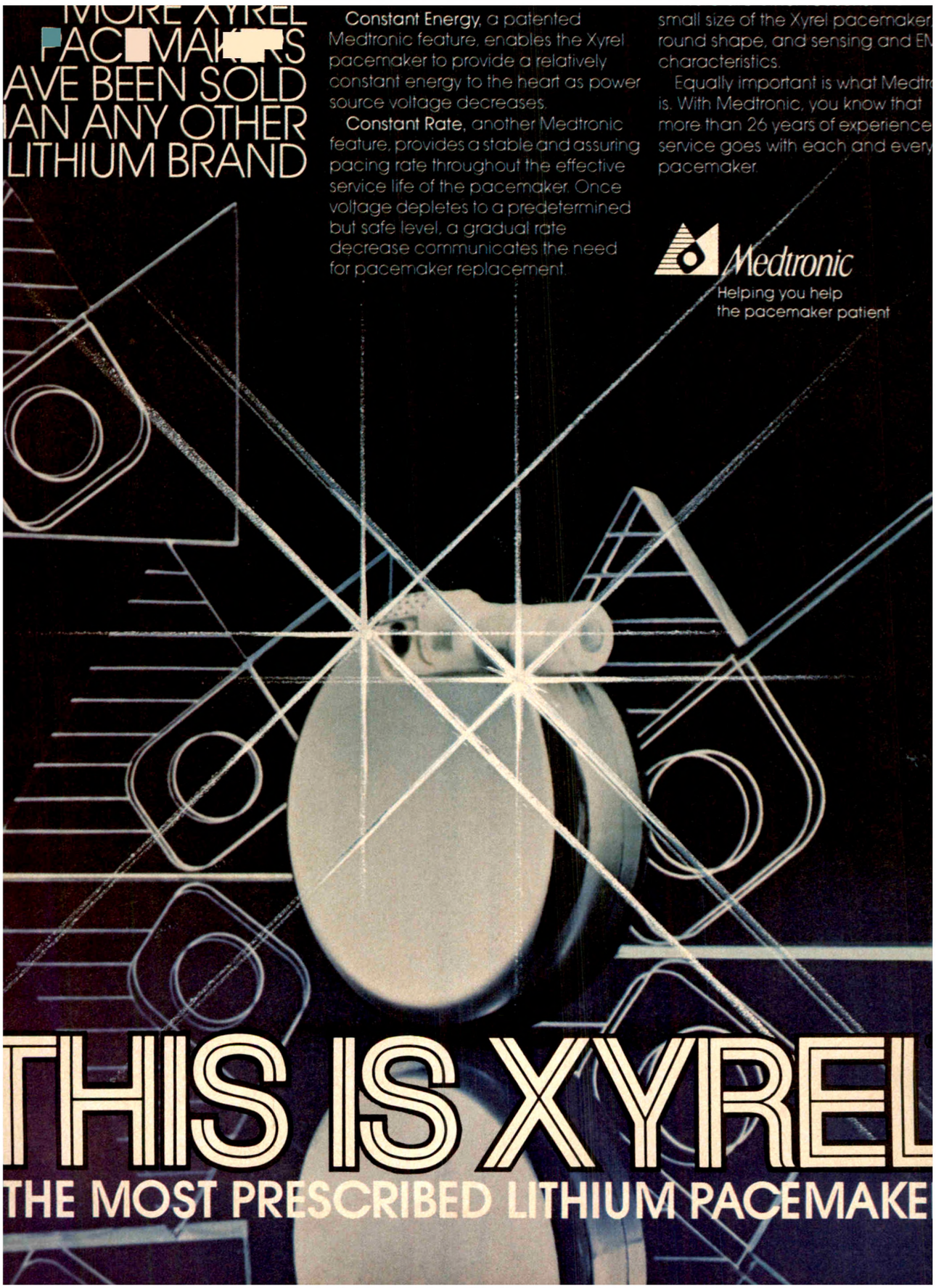
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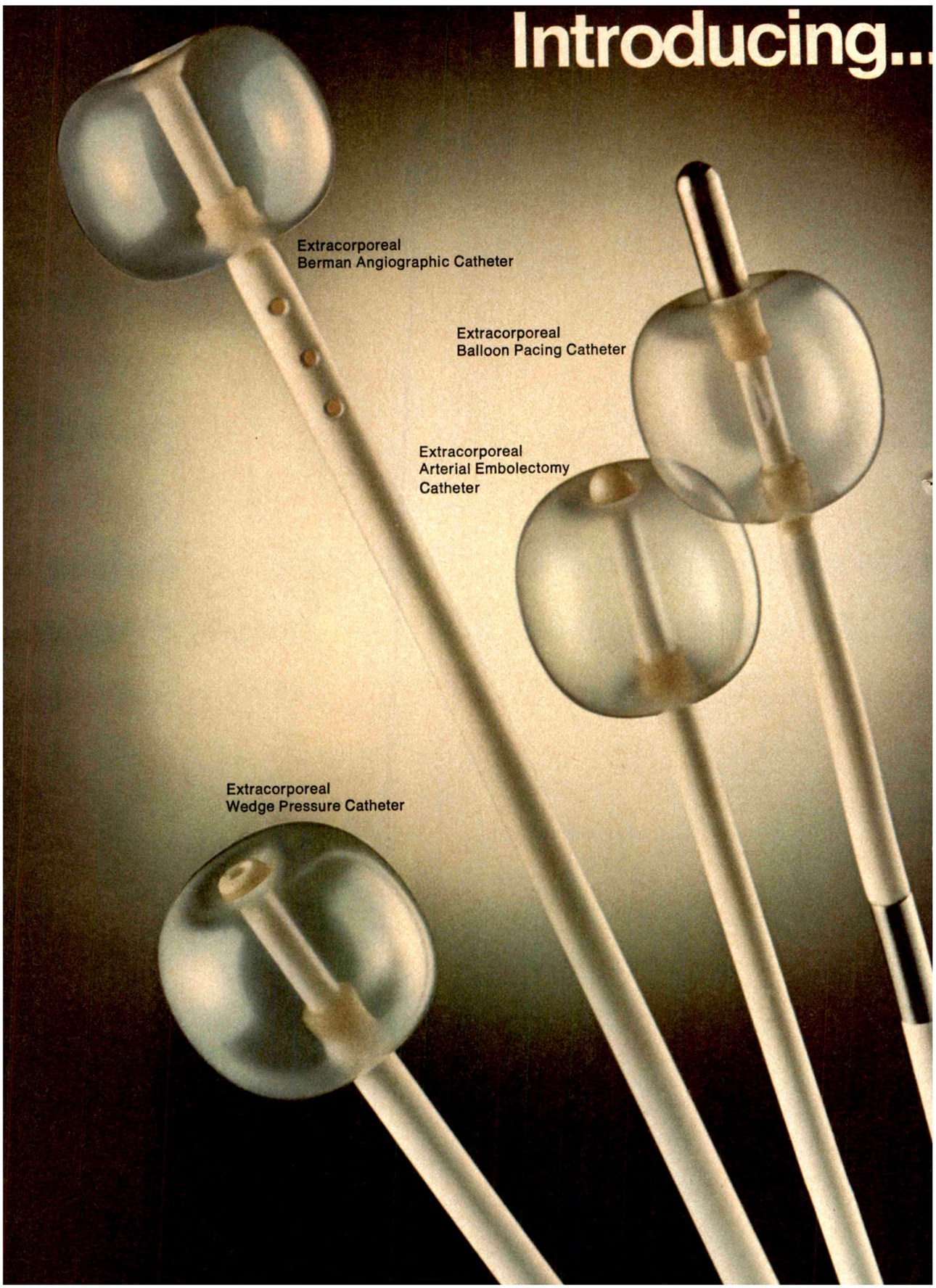
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Letters to the Editor

News From The American Heart Association

A. H. A. Special Report. Prevention of Bacterial Endocarditis: A Statement prepared by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association. Edward L. Kaplan, M.D., Chairman; Bascom F. Anthony, M.D., Alan Bisno, M.D., David Durack, M.D., D. Phil., Harold Hauser, M.D., H. Dean Millard, D.D.S, Jay Sanford, M.D., Stanford T. Shulman, M.D., Max Stillerman, M.D., Angelo Taranta, M.D., Nanette Wenger, M.D.

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

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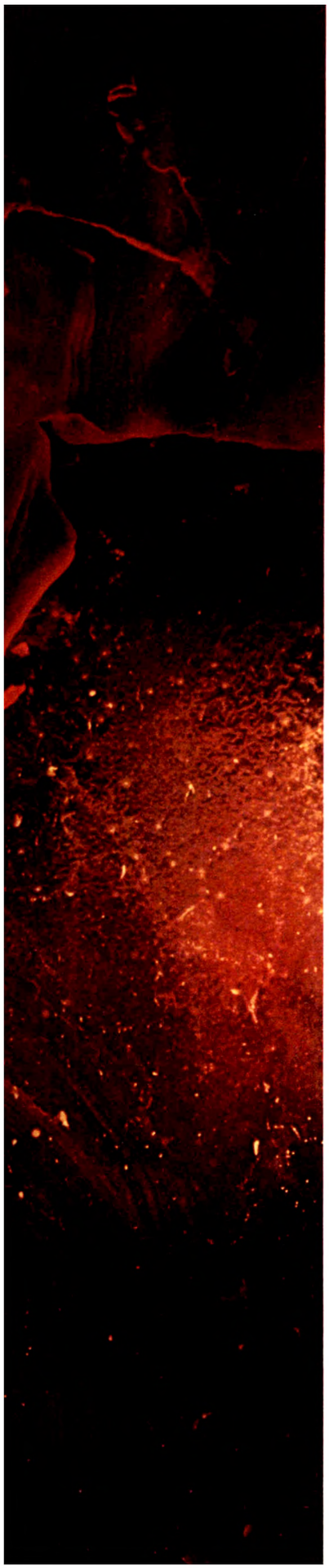


A Broken Heart

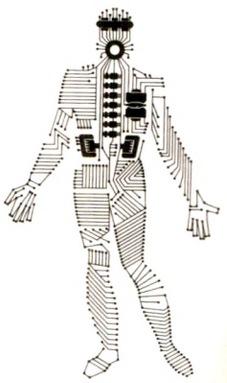
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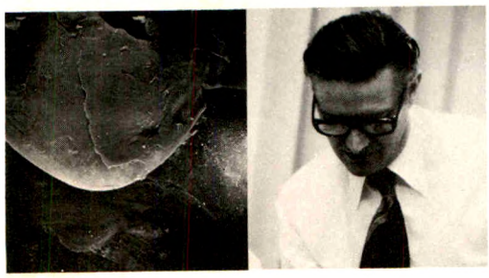
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*Doses as high as this have rarely been employed.

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

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For complete details, please see full prescribing information.

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Reference: 1. Data on file at Boehringer Ingelheim Ltd.

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WAVELESS PULMONARY CAPILLARY WEDGE PRESSURE TRACING IN COR TRIATRIATUM

The clinical and hemodynamic diagnosis of cor triatriatum-subdivided left atrium is fairly difficult.[1] If no communication exists between the right and left atria, selective injection cannot be performed, and angiographic demonstration of the fibromuscular membrane that divides the left atrium may be impossible, as in the following case.

Case report: An 18 year old man was admitted to this institute because of severe hemoptysis. On examination a holosystolic murmur was heard and the clinical and radiologic signs for postcapillary pulmonary hypertension were found.

On cardiac catheterization no communication between the right and left heart chambers was demonstrated and high pulmonary arterial (100/65 mm Hg) and pulmonary capillary wedge (mean 40 mm Hg) pressures were measured. No *a* or *v* waves could be demonstrated in the pulmonary capillary wedge pressure tracing with use of a conventional but well flushed no. 8F catheter-transducer system. However, on withdrawal of the catheter tip into the pulmonary artery, a fairly good quality pulmonary arterial pressure curve was registered, thus demonstrating the good frequency response of the measuring system. This procedure was repeated several times with the same result (Fig. 1).

On angiocardiography, the dividing membrane in the left atrial cavity could not be demonstrated, but the two parts of the left atrium could be distinguished by their pattern of motion. The proximal (high pressure) portion of the left atrium showed no movement, whereas the distal (low pressure) portion manifested a hyperkinetic movement synchronous with the P waves of the electrocardiogram. The diagnosis was later proved at operation.

In our case the waveless pulmonary wedge pressure tracing provided support for assuming that a stenosis existed between the measuring catheter and the contracting left atrium. This observation can be useful in the diagnosis of subdivided left atrium.

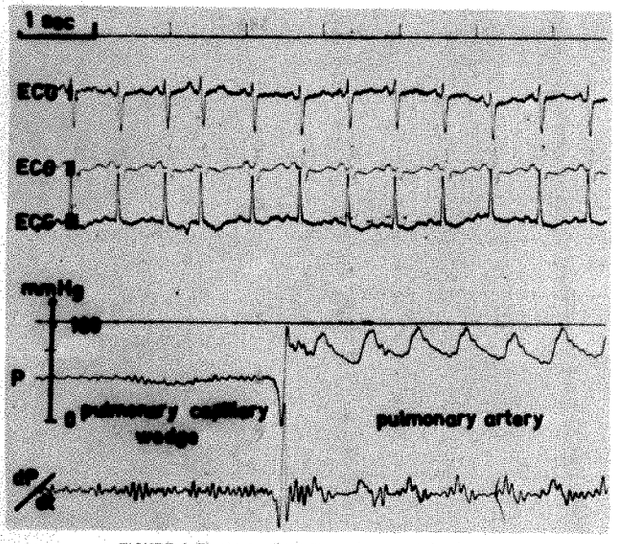


FIGURE 1. Electrocardiograms and pressure tracings.

Mátyás Keltai, MD
Hungarian Institute of Cardiology
Budapest, Hungary

Reference

1. **Thilenius OG, Bharati S, Lev M:** Subdivided left atrium: an expanded concept of cor triatriatum sinistrum. Am J Cardiol 37:743–752, 1976

REPLY

Keltai's letter implies that the proximal high pressure left atrial chamber of tri-atrial hearts has only minimal pressure fluctuations, resulting in a "waveless" pulmonary wedge pressure tracing. This phenomenon can be expected only in patients who have a small obstructive communication between the proximal and distal chamber; it does not differentiate obstruction within the left atrium from obstruction of the pulmonary venous ostia.

There has been almost no published information on the phasic behavior of the pulmonary wedge pressure in cor triatriatum. Maitre et al.[1] reported in their Figures 3 and 9b pulmonary capillary pressures that are indeed waveless. On the other hand, Figure 4 of Michaud et al.,[2] shows an *a* wave of 34 mm Hg that has an x descent of at least 5 mm Hg.

We have found it generally difficult to obtain satisfactory pulmonary wedge pressure recordings in patients with pulmonary hypertension. Such tracings are frequently "waveless," showing only respiratory fluctuations. This waveless appearance is not caused by overdamping but indicates an unsatisfactory location of the wedged catheter tip or possibly severe arteriolar vasoconstriction and obstruction. The interpretation of a nonpulsatile wedge pressure tracing as suggestive of cor triatriatum with obstruction to flow can be maintained only in the presence of other convincing evidence for this rare cardiac malformation.

Otto G. Thilenius, MD, FACC
Department of Pediatrics
The University of Chicago
Chicago, Illinois

References

1. **Maître MJ, Otero E, Querro Jiménez M, et al:** Cor triatriatum. Rev Esp Cardiol 25: 119–128, 1972
2. **Michaud P, Dalloz C, Agé C, et al:** A propos d'un nouveau cas de coeur triatrial de l'adulte, opéré avec succès. Arch Mal Coeur 63:291–300, 1970

MID VENTRICULAR OBSTRUCTIVE CARDIOMYOPATHY VERSUS VENTRICULAR ANEURYSM

Rao,[1] arguing that left ventricular dyskinesia is a misnomer, presents a left ventriculogram in systole and diastole showing an apparent aneurysm. I contend that the example given is not an aneurysm. Mid ventricular obstruction, as a variant of obstructive cardiomyopathy, has been discussed in a case report by Falicov et al.[2] and an abstract presented by my group[3] at the 49th session of the American Heart Association. In this entity, the level of intraventricular obstruction is in the

mid ventricular area, sometimes quite close to the apex rather than the outflow tract. Mid ventricular myectomy is now considered the operation of choice but resection of the apical chambers in cases in which the level of obstruction is close to the apex may prove useful. This variant of obstructive cardiomyopathy should not be mistaken for ventricular aneurysm, which is seen in patients with coronary artery disease. The coronary angiograms in these patients are usually normal.

S. Massoud Alipour
Queen Pahlavi Foundation
Cardiovascular Center
Tehran, Iran

References

1. **Rao G:** Dyskinesia of left ventricle is a misnomer. Am J Cardiol 36:978, 1975
2. **Falicov RE, Resnekov L, Bharati S, et al:** Mid-ventricular obstruction: a variant of cardiomyopathy. Am J Cardiol 37:432–437, 1976
3. **Eslami B, Aryanpurij I, Shakibi J, et al:** Mid-ventricular obstruction. Circulation 53, 54:Suppl II:II-106, 1976

REPLY—I

I disagree that the angiogram shown does not reveal an aneurysm. As I measure the diameter of the ventricular volume, there is no diminution in size along the contracting portion of the ventricle; thus one can dismiss the idea of obstruction. Second, this patient had no pressure gradient along the ventricular channels, as measured during cardiac catheterization. Third, this was a second ventriculogram following severe disease of the left anterior descending coronary artery for which a graft was inserted. For some reason the graft became occluded and acute myocardial infarction developed that led to ventricular aneurysm. The clips in the photographs document this story. In addition, when the aneurysm was resected there was no paradoxical motion, and it was a fibrous tissue documented by histologic sections by a pathologist. Therefore, since this patient did not meet any of the criteria cited by Alipour, I believe that this is not a case of mid ventricular obstructive cardiomyopathy but an aneurysm not dyskinesia. It is only a misunderstanding, not a misdiagnosis.

Gopal Rao, MD
Shadyside Hospital
Pittsburgh, Pennsylvania

REPLY—II

Alipour makes a suggestive point about Rao's case being one of obstructive myocardiopathy as opposed to apical aneurysm due to coronary artery disease. I don't think, however, that he can make that statement with certainty without an actual pressure gradient measured across the area of narrowing. I believe that the ventriculogram in Rao's letter could be from a patient who had coronary disease, left ventricular akinesia or aneurysm and compensatory hypertrophy of the unaffected myocardium producing an hourglass appearance of the ventricular silhouette due to papillary muscle hypertrophy and hypercontractility.

In summary, I believe that Alipour has made a suggestive, but by no means proved, case for mid ventricular cardiomyopathy in a patient with apical contraction abnormalities.

Raul E. Falicov, MD, FACC
Section of Cardiology
Christ Hospital
Oak Lawn, Illinois

ECHOCARDIOGRAM IN AORTIC STENOSIS

In Table II of Glanz et al.,[1] the mean value of the derived pressure constant k was incorrectly calculated in 12 of 16 cases. Interestingly, the following corrections (Table A) change only the standard deviation of the mean value of k (from ±6.7 to ±8.4).

In their Table III, errors occurred in the ratio between end-systolic and end-diastolic wall thickness (Ws/Ds) (5 of 13 cases) and the echocardiographic estimate of left ventricular pressure (11 of 13 cases). The corrections shown in Table B further improve the excellent correlation between the estimated and directly measured left ventricular peak systolic pressure. Although the errors cited do not impair the quality of the paper or its final conclusions, I believe that such discrepancies are unacceptable in an important journal.

Roberto Bassan, MD
Cardiac Catheterization Laboratory
Hospital de Bonsucesso-I.N.P.S.
Rio de Janeiro, Brazil

TABLE A

Published and Corrected Values for the Constant k

Case no.	Published	Corrected
1	220	220
2	217	216
3	211	213
4	230	230
5	235	233
6	238	242
7	222	227
8	223	227
9	220	220
10	230	230
11	225	224
12	229	228
13	223	228
14	224	205
15	223	229
16	226	224
Mean	224.75	224.75
SD	±6.7	±8.37

SD = standard deviation.

TABLE B

Corrected Values for Ws/Ds Ratio and Echocardiographic Estimate of Left Ventricular Pressure

Case no.	Ws/Ds Ratio		Left Ventricular Pressure		
			By Echocardiogram		By Catheter
	Published	Correct	Published	Correct	
1	0.83	0.81	180	182	190
2	1.10	1.09	245	245	220
3	0.50	0.50	115	112	120
4	0.67	0.67	150	151	140
5	0.48	0.48	108	108	115
6	0.75	0.75	167	169	180
7	0.48	0.48	115	108	130
8	0.53	0.53	120	119	110
9	0.71	0.71	165	160	155
10	0.56	0.57	125	128	140
11	0.69	0.67	155	151	140
12	0.70	0.70	165	157	152
13	0.66	0.65	150	146	140
Mean	. . .	. . .	151	149	149

Ws/Ds ratio = ratio between end-systolic and end-diastolic wall thickness.

Reference

1. **Glanz S, Hellenbrand WE, Berman MA, et al:** Echocardiographic assessment of the severity of aortic stenosis in children and adolescents. Am J Cardiol 38:620–625, 1976

REPLY

The minor errors in Tables II and III are readily explainable. Upon initial submission of the original manuscript, the tables included ratios between end-systolic (Ws) and end-diastolic (Ds) wall thickness but not their individual values. When the editors asked for inclusion of these data, the echocardiograms were remeasured and a difference from the initial values of ±1.0 mm apparently occurred. However, the calculated k value in Table II, the predicted left ventricular pressure in Table III and the ratios in both tables were not recalculated.

This resulted in the discrepancies that Bassan rightfully points out. We are pleased to find the correlation coefficient improved but would be satisfied with the *r* value stated in the article. Since publication, we have seen six additional patients with severe aortic stenosis, and the correlation continues to be excellent.

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CARDIAC ARRHYTHMIAS AFTER PSYCHOTROPIC DRUGS

Fowler et al.[1] described eight patients who experienced cardiac manifestations while receiving psychotropic drugs. In five of these patients the cardiac event was life-threatening, and in one resulted in death. The patients are described as "receiving usual therapeutic doses of psychotropic agents."

I question whether the drug regimens for most of these patients were usual or therapeutic. One patient had an electrocardiographic change after an overdose with imipramine and trifluoperazine. Three patients were receiving daily doses of thioridazine of 1,000 to 1,600 mg. Six of the eight patients were receiving polypharmaceutical regimens, four of which involved combinations of antipsychotic drugs. One patient was receiving 1,600 mg daily of thioridazine, 800 mg daily of mesoridazine, biweekly fluphenazine injections and benztropine.

The largest daily dose of thioridazine recommended by the Food and Drug Administration and all authorities in psychopharmacology is 800 mg. This "ceiling" dose of thioridazine is primarily because of the danger of pigmentary retinopathy, but thioridazine has the highest anticholinergic potency of currently available antipsychotic drugs and has the greatest effects on cardiac repolarization. Furthermore, while polypharmacy in general should be used with caution, there is little to recommend combinations of antipsychotic drugs.[2] The patient given three antipsychotic drugs plus an antiparkinson drug was being subjected to an extreme anticholinergic blockade.

A final point is trivial but indicates the lack of attention to psychopharmacology in this paper. The 2 cc intramuscular injection of fluphenazine received by Patient 3 every other week was undoubtedly the enanthate of decanoate rather than the hydrochloride.

This article contains a valuable review of the cardiotoxicity of psychotropic drugs and will be an important reference. It would be unfortunate, however, if physicians were to confuse toxic doses of psychotropic drugs with normal therapeutic doses. Proper education of physicians in psychopharmacology may provide some degree of primary prevention of these cardiac abnormalities.

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2. **Hollister LE:** Clinical Use of Psychotherapeutic Drugs. Springfield, Ill, Charles C Thomas, 1973, p 40–42

REPLY

Although our paper emphasizes the occurrence of arrhythmias in patients receiving usual therapeutic doses of psychotropic drugs, it does not state that the report is limited to those receiving doses recommended by the Food and Drug Administration. In fact, Patients 2, 6, 7 and 8 were receiving drugs in doses within the range recommended by that agency.

Use of the word "therapeutic" in the paper was meant to indicate that the drugs were given to the patients for therapy and were not taken by the patients accidentally or intentionally without supervision. We agree that the doses received by some of the patients exceeded those generally recommended. However, larger doses have been used in severely ill patients. For example, in the report by Hollister and Kosek,[1] Patient 5 was given 1,200 mg of thioridazine and 1,500 mg of chlorpromazine daily; Patient 6 was given 1,600 mg of thioridazine, or 2,400 mg of chlorpromazine four times daily. Even larger doses (3,600 mg four times daily) of thioridazine or chlorpromazine were used in the cases described by Kelly et al.[2] and Giles et al.[3]

Surely Gelenberg does not believe that patients who are severely disabled and who do not respond to the officially recommended dosages of drugs do not in some instances receive larger doses. Has he inquired concerning therapeutic regimens used to treat long-term patients in mental hospitals in his own community?

Our paper was not intended to recommend excessive amounts or numbers of drugs; it is a report of serious and life-threatening cardiac arrhythmias complicating both usual and unusual amounts of psychotropic drugs.

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VECTORCARDIOGRAPHIC CRITERIA FOR DIAPHRAGMATIC MYOCARDIAL INFARCTION

Stein and Simon[1] have examined the usefulness of vectorcardiographic criteria for diaphragmatic myocardial infarction. In addition to confirming the utility of Young and Wil-

liams' criteria,[2] they suggest two new criteria. They particularly emphasize the usefulness of a ratio greater than 0.22 between the 0 to left x-intercept vector and the maximal QRS vector. In using this measurement, we found that patients with left anterior hemiblock and without evidence of diaphragmatic infarction commonly have ratios exceeding 0.22. Review of classic vectorcardiograms (such as those in the textbook of vectorcardiography by Chou et al.[3]) confirmed our observation. Furthermore, many patients with leftward and counterclockwise loops (with or without left ventricular hypertrophy) will also have ratios greater than 0.22. Stein and Simon did not indicate that the direction of rotation was important in using this criterion. We suggest that proper utilization of this criterion requires that (1) the direction of initial rotation be clockwise, or (2) that the 0.01 second vector be located superiorly. With this modification, Stein and Simon's criterion should be as useful as their studies have indicated.

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References

1. **Stein PD, Simon AP:** Vectorcardiographic diagnosis of diaphragmatic myocardial infarction. Am J Cardiol 38:568–575, 1976
2. **Young E, Williams C:** The frontal plane vectorcardiogram in old inferior myocardial infarction. Criteria for diagnosis and electrocardiographic correlation. Circulation 37:604, 1968
3. **Chou T, Helm RA, Kaplan S:** Clinical Vectorcardiography, second edition. New York, Grune & Stratton, 1974

REPLY

We believe that there is confusion related to the definition of the criteria that we indicated were useful. In our article, the 0 to left x-intercept was defined as the maximal leftward displacement of *superior* forces. This definition indicates that initial forces must be superior in order to measure a 0 to left x-intercept greater than 0. Consequently, the ratio in the frontal plane of the 0 to left x-intercept to the maximal QRS refers to the ratio of the maximal leftward displacement of *superior* forces to the maximal QRS. The numerator of the ratio refers exclusively to the leftward displacement of superior forces. With the correct criteria in mind, it is apparent that none of the typical vectorcardiograms of left anterior hemiblock that were illustrated by Chou and associates (Fisher and Mugmon's Ref. 3) satisfy the criteria of diaphragmatic infarction that we described. Similarly, patients with counterclockwise frontal QRS loops could have ratios of the 0 to left x-intercept maximal QRS greater than 0.22 only if the entire loop were superior.

The criteria we described will result in some false positive diagnoses in patients with other types of heart disease. We have observed false positive diagnoses in right ventricular hypertrophy, occasional instances of left anterior hemiblock in which initial forces are superior, the Wolff-Parkinson-White syndrome and idiopathic hypertrophic subaortic stenosis. It is well known that the electrocardiograms and vectorcardiograms of such patients may simulate a myocardial infarction.

We thank Fisher and Mugmon for the opportunity of emphasizing an important aspect of the definitions that apparently could be misunderstood.

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Armando P. Simon, MD, FACC
Veterans Administration Hospital
Wichita, Kansas

BOOKS RECEIVED

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An Introduction to Electrocardiography, fifth edition, by Leo Schamroth, MD. Oxford, London, Edinburgh, Melbourne, Blackwell Scientific (American distributor: J. B. Lippincott, Philadelphia), 1976, 240 pages, $10.00

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MD. New York, David McKay, 1977, 256 pages, $14.95

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Translations in Respiratory Physiology, edited by John B. West, MD, PhD. Stroudsburg, Pennsylvania, Dowden, Hutchinson and Ross, 1976, 772 pages, $28.00

You and Your Heart, by Paul Kezdi, MD. New York, Atheneum, 1977, 245 pages, $8.95

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For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

President's Page: International Education



Dr. Mason

The College's major role as the leading professional society in continuing cardiovascular education is extended to the international level by its Circuit Course programs to foreign countries. The overseas Circuit Courses were initiated in 1961 by the College's International Education Committee, chaired by Dr. Eliot Corday, and the first visits were made to the Philippines and Taiwan. During the past 17 years, the College has conducted 43 Circuit Course programs whose faculties have visited 41 developing countries. Supported by the Bureau of Education and Cultural Affairs of the United States State Department, these programs have had invaluable impact and have resulted in lasting friendships between our physicians and those of the host countries.

Organization of these courses requires substantial advance planning by the International Education Committee and considerable commitment of time by the participating faculty and their spouses. The American physicians are selected by the medical societies of the countries to be visited and the faculty team generally consists of four members—two adult cardiologists, one pediatric cardiologist and one cardiovascular surgeon. The Circuit Course tour provides the medical communities of usually three nations with intensive five day continuing education programs in cardiovascular diseases. Since the inception of the program, nearly 200 College members have participated, devoting an average of 20 days from their offices.

The latest Circuit Course, no. 43, visited Finland, Poland and Czechoslovakia from May 17 to June 4, 1977. Constituting the American delegation were Drs. John J. Collins, Jr., Samuel Kaplan, Charles E. Rackley and I and our wives. We received the warmest of welcomes and were afforded exceptional kindness and generosity by the local arrangements committees in each of the five cities we visited. Our principal hosts were Dr. Kimmo Luomanmaki, president of the Finnish Cardiac Society; Dr. Kalevi Pyorala, past president of the Finnish Cardiac Society; Dr. Jan Kwoczynski, president of the Polish Cardiological Society; Dr. Wladyslaw Krol, president of the Cracow Branch of the Polish Cardiological Society; Dr. Zdenek Reinis, president of the Czechoslovakian Society of Cardiology; and Dr. Frantisek Kolbel, secretary of the Czechoslovakian Society of Cardiology.

The American cardiologists conducted symposia at the Meilahti University Center Hospital in Helsinki, the University Central Hospital in Kuopio, the Nicolaus Copernicus Medical Academy in Cracow, the Polish Academy of Science in Warsaw and the Charles University in Prague. The scientific sessions were extremely well attended by enthusiastic physicians in each city. We were genuinely impressed by the high standards of cardiovascular patient care and particularly the strong interest in modern cardiology shown by our knowledgeable foreign colleagues.

There is no question that the College's International Educational Program is a uniquely successful activity that should be continued and augmented in the future. This program provides the means for exchange of knowledge between the visiting faculty and physicians in host countries and affords the medical communities of participating nations opportunities for continuing education. Moreover, the Circuit Courses have established cooperative relations among physicians, governments and people of many countries and have united across national borders those concerned with the treatment of heart disease.

Dean T. Mason, MD, FACC
President
American College of Cardiology

Calendar of Continuing Medical Education Programs

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

AUGUST THROUGH DECEMBER 1977

1977

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, CA

SEPT. 7–10 — **Core Curriculum: Interpretation and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, directors. Philadelphia Marriott Motor Hotel, Philadelphia, PA

SEPT. 29–30 — **Cardiac Electrophysiology for a Cardiologist.** Borys Surawicz, FACC and Leonard S. Gettes, FACC, directors. Continental Inn, Lexington, KY

OCT. 3–5 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 6–8 — **New Diagnostic and Therapeutic Approaches in Cardiology—1977.** Edmund H. Sonnenblick, FACC and James E. Scheuer, FACC, co-directors. The Plaza, New York, NY

OCT. 10–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 11–14 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

OCT. 13–15 — **New Techniques and Concepts in Cardiology: Pathogenesis and Treatment of Coronary Artery Disease; Sudden Death Without Coronary Disease.** Stephen E. Epstein, FACC, director. The Washington Hilton Hotel, Washington, DC

OCT. 13–15 — **The Clinical Spectrum of Adult Heart Disease.** Jonathan Abrams, FACC, director and Paul T. Cochran, FACC, co-director. University of New Mexico School of Medicine, Basic Medical Sciences Building, Albuquerque, NM

OCT. 21–23 — **Practical Cardiology—1977.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt Hotel, Monterey, CA

NOV. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, co-directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

NOV. 8–10 — **Clinical Perspectives in Valvular and Ischemic Heart Disease.** James T. Mazzara, FACC, director and Richard J. Kennedy, FACC, co-director. St. Vincent's Hospital and Medical Center of New York, New York, NY

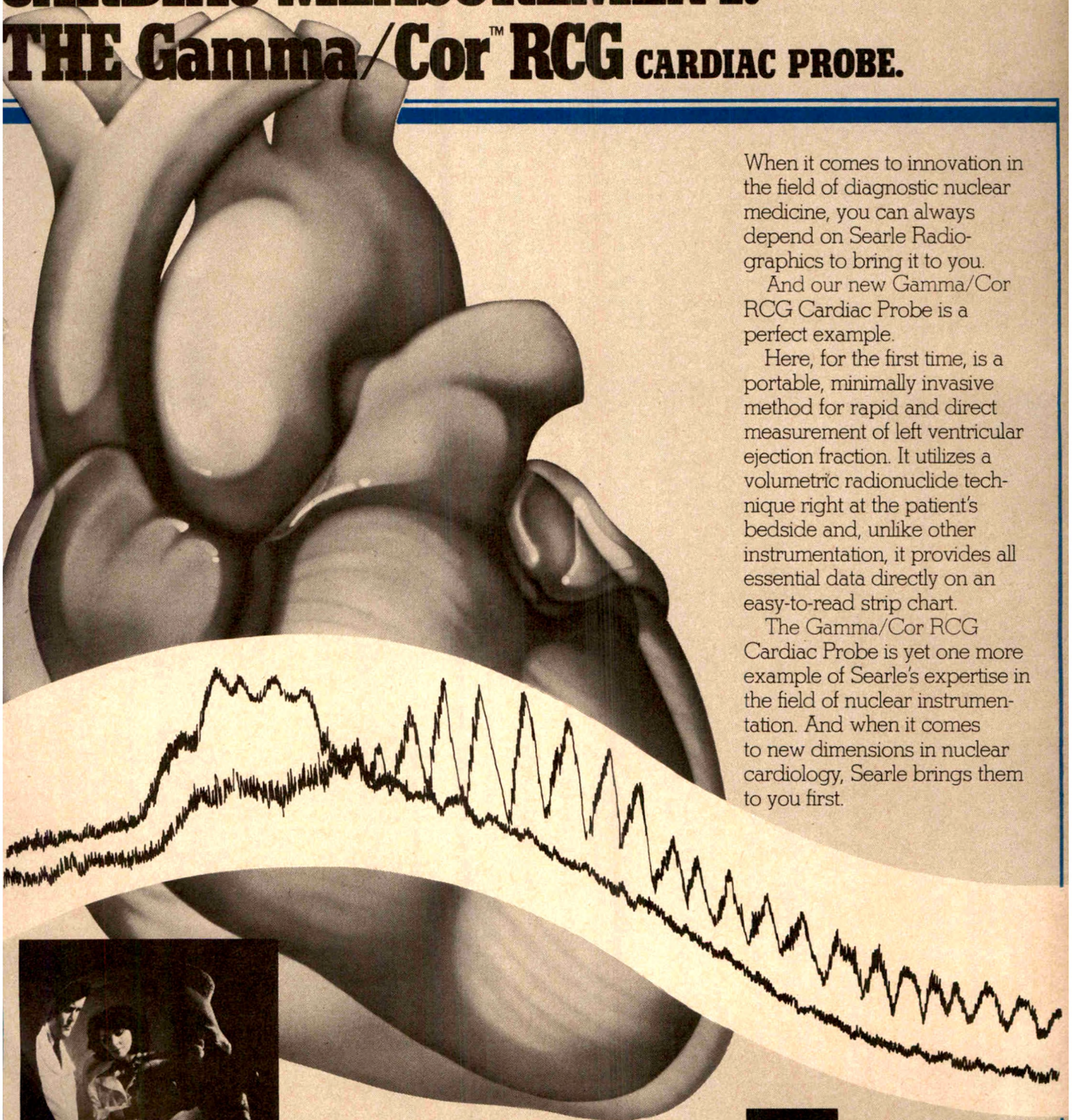
NOV. 20–23 — **Coronary, Valvular and Myocardial Heart Diseases: Structure-Function Correlations and Implications for Therapy.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, VA

DEC. 2–4 — **Advances in Heart Disease—1978.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 9–11 — **Tenth Annual Cardiovascular Symposium: Theory and Practice of Cardiology Today.** Henry I. Russek, FACC, director. Americana Hotel, New York, NY

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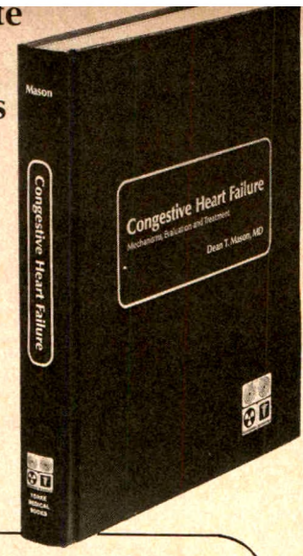
CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.
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PRECAUTIONS: Administer with caution and adjust to the requirements of the individual patient. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
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Dean T. Mason, M.D.

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

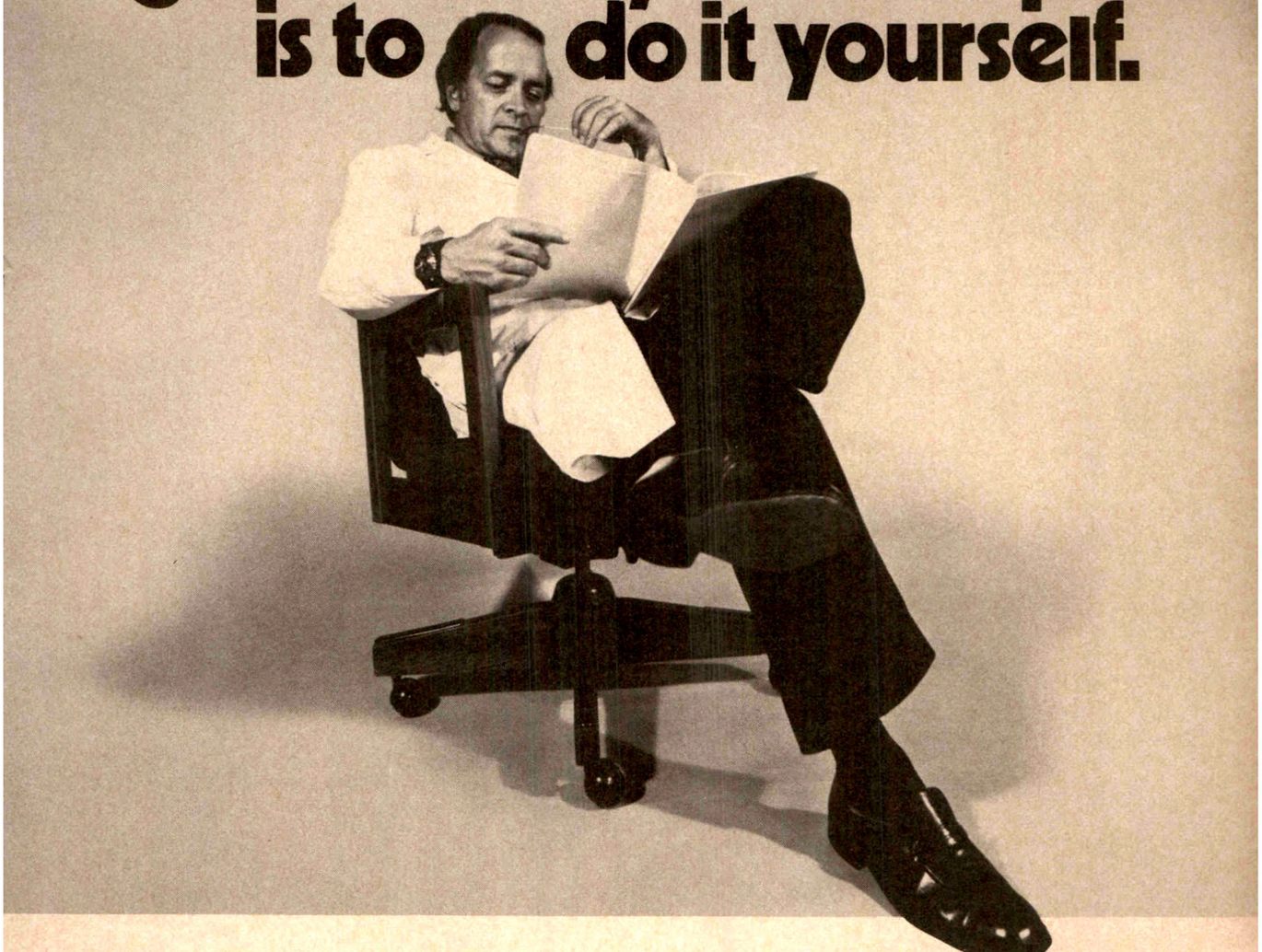
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Description: Each tablet of Peritrate SA Sustained Action contains: pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.
Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.
This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.
Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrites and nitrates may occur.
Adverse Reactions: Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.
In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:
(a) Cutaneous vasodilatation with flushing.
(b) Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
(c) An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.
Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
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Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the post-arteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
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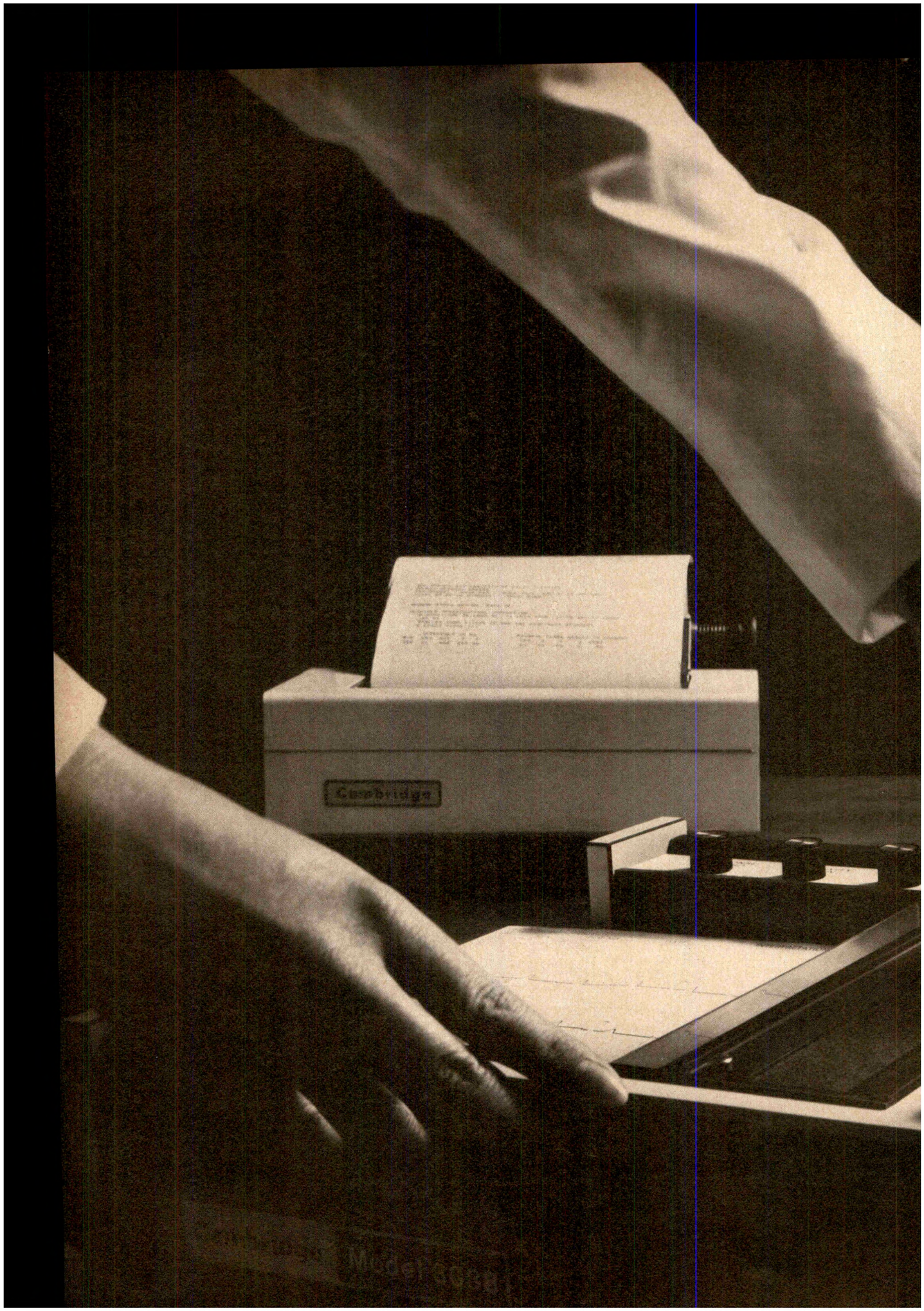
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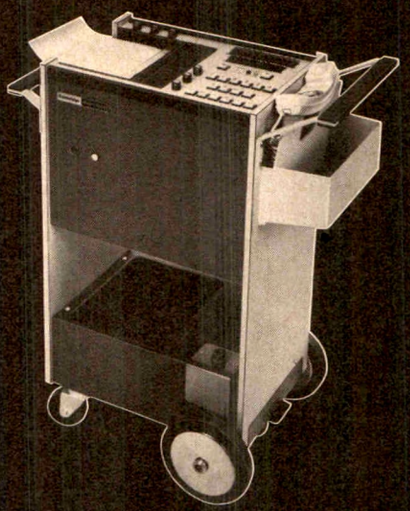
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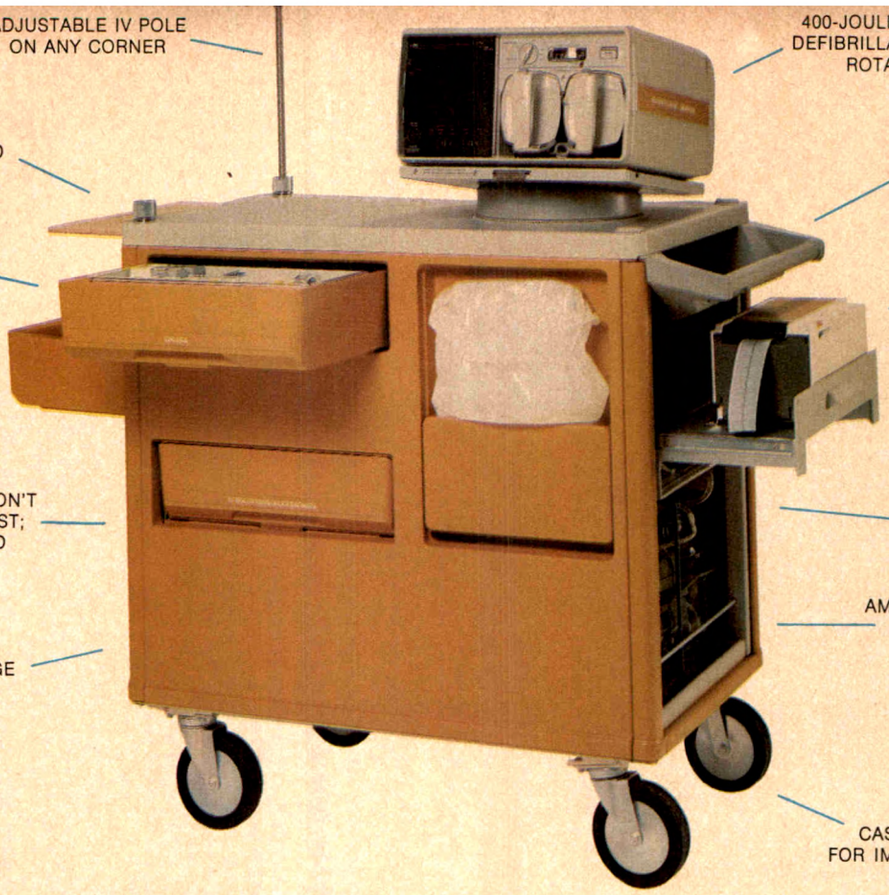
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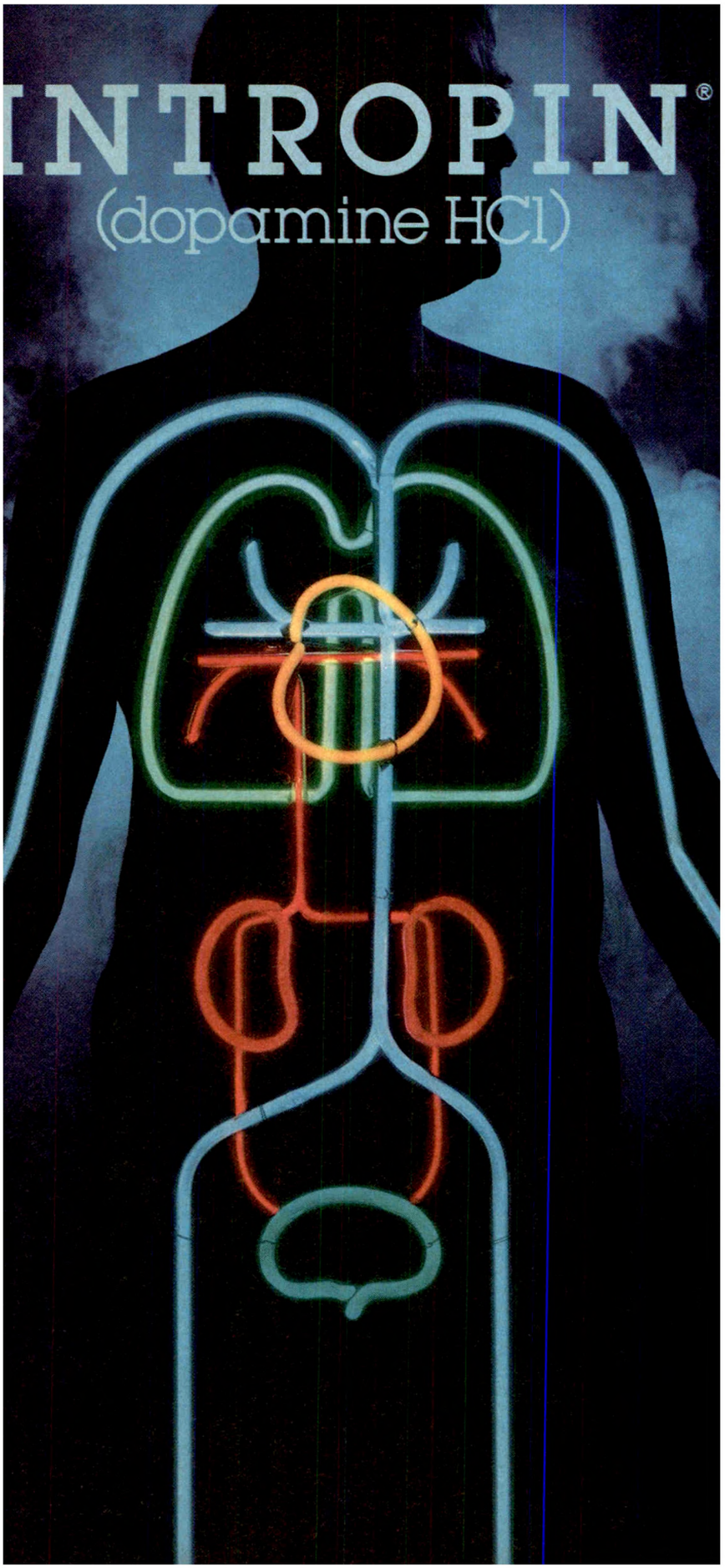
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The unique ability of Intropin to act on the "dopaminergic" receptors in the mesenteric and renal vasculature causes vasodilation in these beds and leads to increased renal blood flow, glomerular filtration rate and urine output. At low dose levels (less than 5 mcg/kg/min), when cardiac stimulation is not usually observed, these increases are independent of increased cardiac output.

In comparison, norepinephrine causes vasoconstriction in these beds, further compromising vital organ function.[1] Isoproterenol causes generalized systemic vasodilation (thereby requiring greater cardiac output to increase vital organ perfusion) and does not increase the renal fraction of the increased cardiac output.[2]

Increases cardiac output

At higher doses (above 5 mcg/kg/min), Intropin begins to increase myocardial contractility, stroke volume and cardiac output by direct positive inotropic effect while maintaining much of the unique dopaminergic effect. In certain patients such as refractory congestive failure patients, the increase in cardiac output may be seen at doses of less than 5 mcg/kg/min.

Norepinephrine, on the other hand, has a similar inotropic effect, but the expected increase in cardiac output is often diminished due to the increased systemic vascular resistance (afterload) resulting from norepinephrine's alpha adrenergic activity. Isoproterenol increases cardiac output in part through a chronotropic effect.[3] Its use results in a greater increase in myocardial oxygen consumption than does the inotropic effect of Intropin. It also results in a greater potential for arrhythmias.[3] The increased cardiac output obtained with isoproterenol is delivered to the total systemic vasculature due to general vasodilation while the selective vasodilation of Intropin directs more blood supply to the areas in need of vital perfusion.

Increases blood pressure

Intropin doses of over 20 mcg/kg/min will usually result in an alpha adrenergic (vasoconstriction) response in the peripheral vasculature. This usually raises the pressure and also redirects blood flow through the vasodilated vasculature of the renal and mesenteric beds. Thus, Intropin can increase blood pressure through an inotropic cardiac response or at doses above 20 mcg/kg/min through an additional peripheral vasculature response.

References:
1. Rosenblum, R., Am. Heart J., 87:527-530, 1974.
2. Goldberg, L.I., N.E.J. of Med., 291:707-710, 1974.
3. Harrison, D.C., Am. J. of Card., 35:656-659, 1975.

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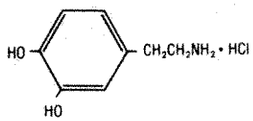
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Each milliliter of sterile, pyrogen-free INTROPIN Injection contains 40 mg. of dopamine hydrochloride (equivalent to 32.96 mg. of dopamine base) in Water for Injection, USP, containing 1% sodium bisulfite as a preservative.

ACTIONS: INTROPIN exerts an inotropic effect on the myocardium resulting in an increased cardiac output. INTROPIN produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with a tachyarrhythmia. Clinical studies indicate that INTROPIN usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Total peripheral resistance at low and intermediate therapeutic doses is usually unchanged. Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. INTROPIN has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolality of the urine.

INDICATIONS: INTROPIN is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander or whole blood should be instituted or completed prior to administration of INTROPIN.

Patients most likely to respond adequately to INTROPIN are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. Multiclinic trials indicate that the shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and INTROPIN, the better the prognosis.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when INTROPIN is administered before urine flow has diminished to levels approximately 0.3 ml./minute, prognosis is more favorable. Nevertheless, in a number of oliguric or anuric patients, administration of INTROPIN has resulted in an increase in urine flow which in some cases reached normal levels. INTROPIN may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output – Increased cardiac output is related to INTROPIN's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favorable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (e.g. femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in systemic vascular resistance as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, INTROPIN's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer INTROPIN as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

Do **NOT** add INTROPIN to any alkaline diluent solution, since the drug is inactivated in alkaline solution.

Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage. Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of INTROPIN. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Usage in Pregnancy – Animal studies have revealed no evidence of teratogenic effects from INTROPIN. In one study, administration of INTROPIN to pregnant rats resulted in a decreased survival rate of the newborn and a potential for cataract formation in the survivors. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of this drug in children has not been established. INTROPIN has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use. Further studies are in progress.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Extravasation may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities. If a change in skin color or temperature occurs and is thought to be the result of compromised circulation to the extremities, the benefits of continued INTROPIN infusion should be weighed against the risk of possible necrosis. This condition may be reversed by either decreasing or discontinuing the rate of infusion.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml. of Saline solution containing from 5 to 10 mg. of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore may sensitize the myocardium to the action of certain intravenously administered catecholamines. This interaction appears to be related both to pressor activity and to beta adrenergic stimulating properties of these catecholamines. Therefore, as with certain other catecholamines, and because of the theoretical arrhythmogenic potential, INTROPIN should be used with EXTREME CAUTION in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

Careful Monitoring Required – Close monitoring of the following indices – urine flow, cardiac output and blood pressure – during INTROPIN infusion is necessary as in the case of any adrenergic agent.

ADVERSE REACTIONS: The most frequent adverse reactions observed in clinical evaluation of INTROPIN included ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Other adverse reactions which have been reported infrequently were aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

DOSAGE AND ADMINISTRATION:

WARNING: This is a potent drug: It must be diluted before administration to patient.

Suggested Dilution – Transfer contents of one ampul (5 ml. containing 200 mg. INTROPIN) by aseptic technique to either a 250 ml. or 500 ml. bottle of one of the following sterile intravenous solutions:

1) Sodium Chloride Injection, USP
2) Dextrose 5% Injection, USP
3) Dextrose (5%) and Sodium Chloride (0.9%) Injection, USP
4) 5% Dextrose in 0.45% Sodium Chloride Solution
5) Dextrose (5%) in Lactated Ringer's Solution
6) Sodium Lactate (1/6 Molar) Injection, USP
7) Lactated Ringer's Injection, USP

These dilutions will yield a final concentration for administration as follows:
250 ml. dilution contains 800 mcg./ml. of INTROPIN
500 ml. dilution contains 400 mcg./ml. of INTROPIN

INTROPIN has been found to be stable for a minimum of 24 hours after dilution in the sterile intravenous solutions listed above. However, as with all intravenous admixtures, dilution should be made just prior to administration.

Do **NOT** add INTROPIN Injection to 5% Sodium Bicarbonate or other alkaline intravenous solutions, since the drug is inactivated in alkaline solution.

Rate of Administration – INTROPIN, after dilution, is administered intravenously through a suitable intravenous catheter or needle. An i.v. drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with INTROPIN. In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration at rates greater than 50 mcg./kg./min. have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, adjustment of drug concentration may be preferred over increasing the flow rate of a less concentrated dilution.

Suggested Regimen:

1. When appropriate, increase blood volume with whole blood or plasma until central venous pressure is 10 to 15 cm H_2O or pulmonary wedge pressure is 14-18 mm Hg.

2. Begin administration of diluted solution at doses of 2-5 mcg./kg./minute INTROPIN in patients who are likely to respond to modest increments of heart force and renal perfusion.

In more seriously ill patients, begin administration of diluted solution at doses of 5 mcg./kg./minute INTROPIN and increase gradually using 5 to 10 mcg./kg./minute increments up to 20 to 50 mcg./kg./minute as needed. If doses of INTROPIN in excess of 50 mcg./kg./minute are required, it is suggested that urine output be checked frequently. Should urine flow begin to decrease in the absence of hypotension, reduction of INTROPIN dosage should be considered. Multiclinic trials have shown that more than 50% of the patients were satisfactorily maintained on doses of INTROPIN less than 20 mcg./kg./minute. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of INTROPIN may be employed in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of the blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of INTROPIN should be adjusted according to the patient's response, with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices for decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

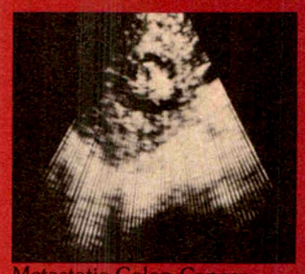
OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since INTROPIN's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED: 5 ml. ampuls containing 40 mg. dopamine HCl per milliliter. September, 1975

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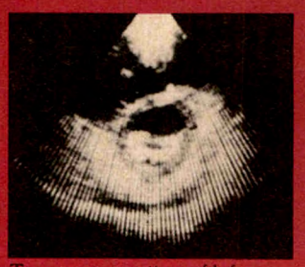
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Transverse section of left ventricle with stenotic mitral valve.

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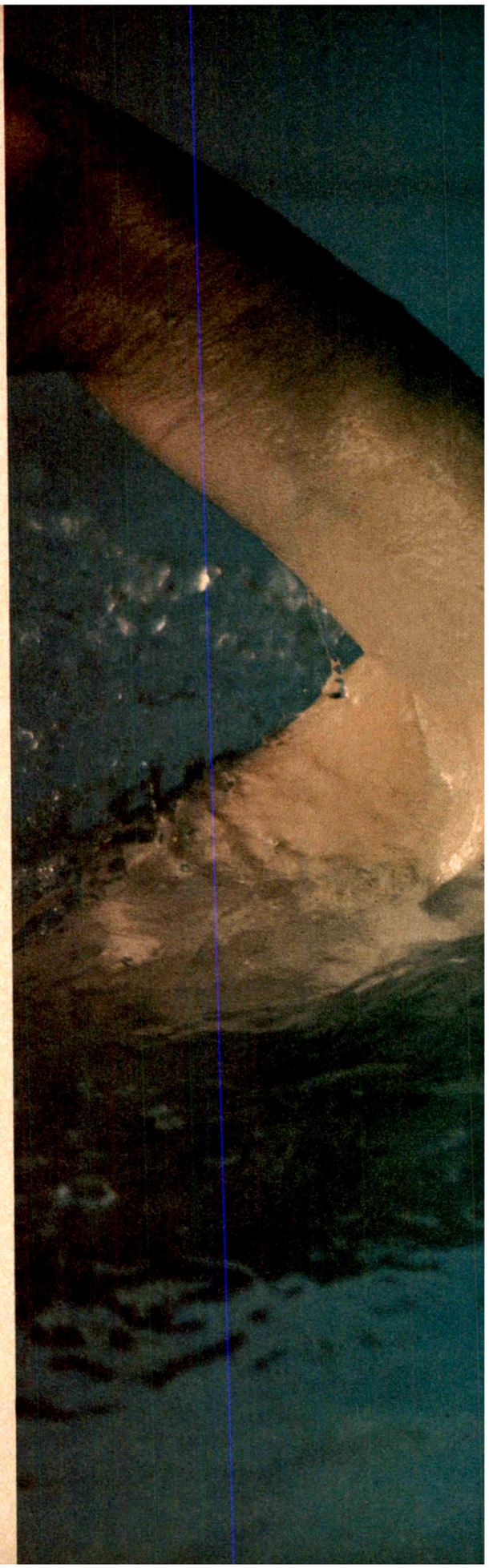


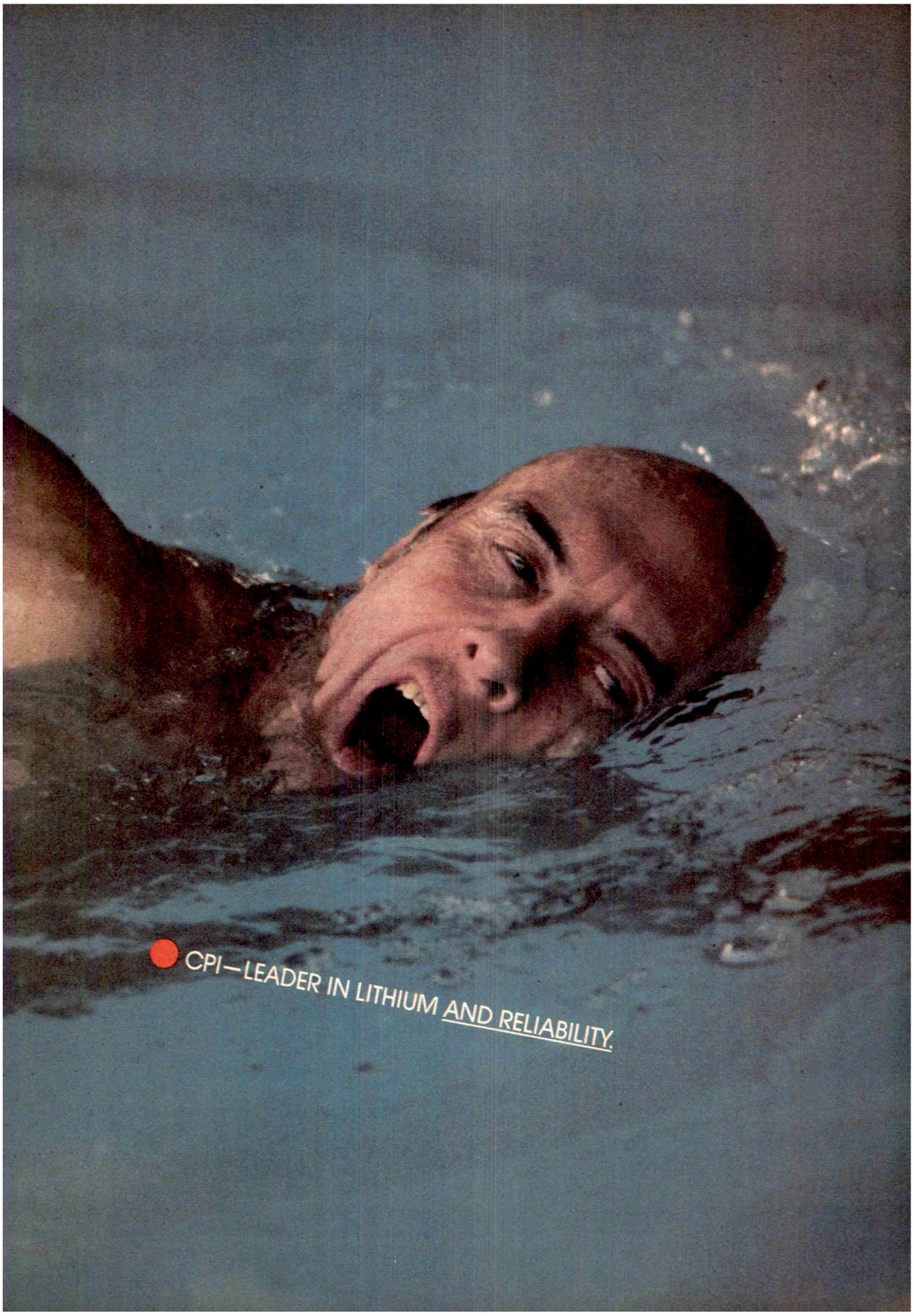
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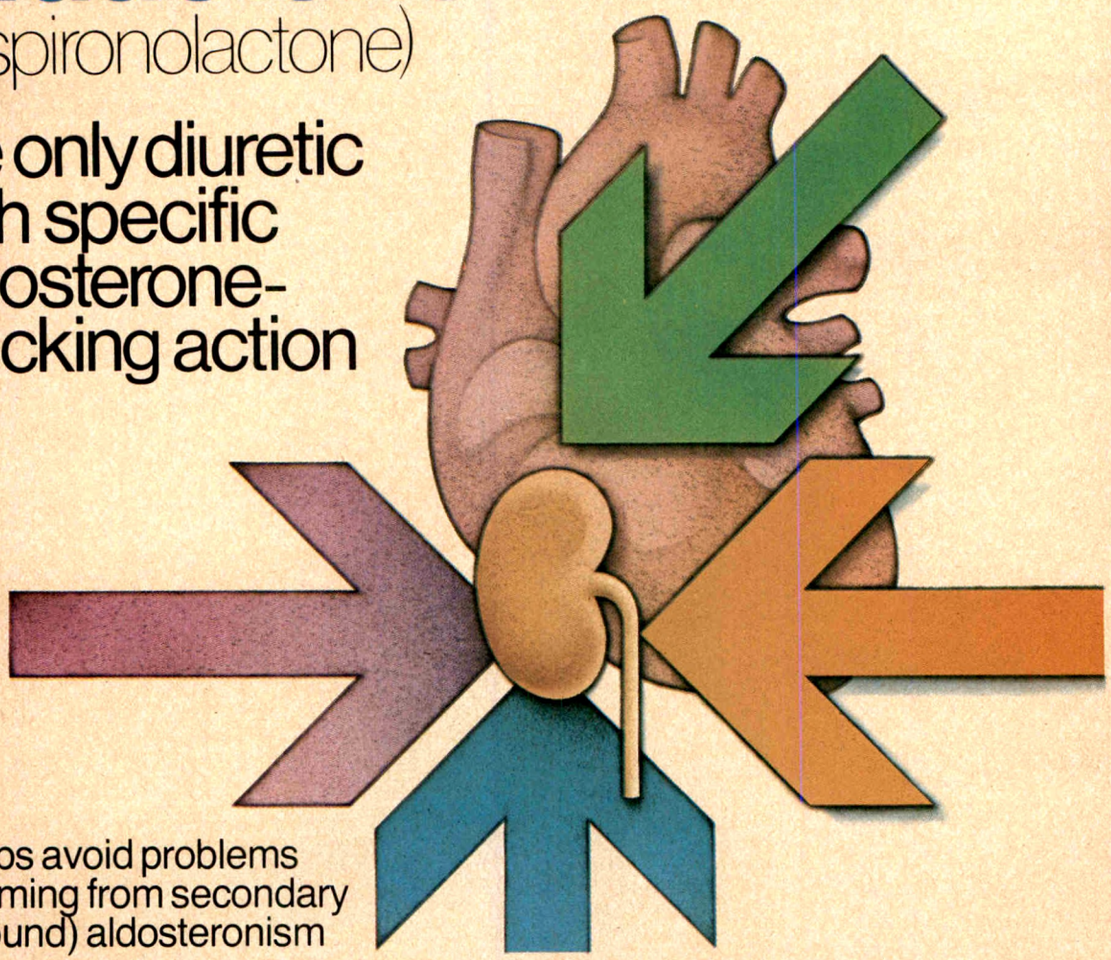
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WARNING

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Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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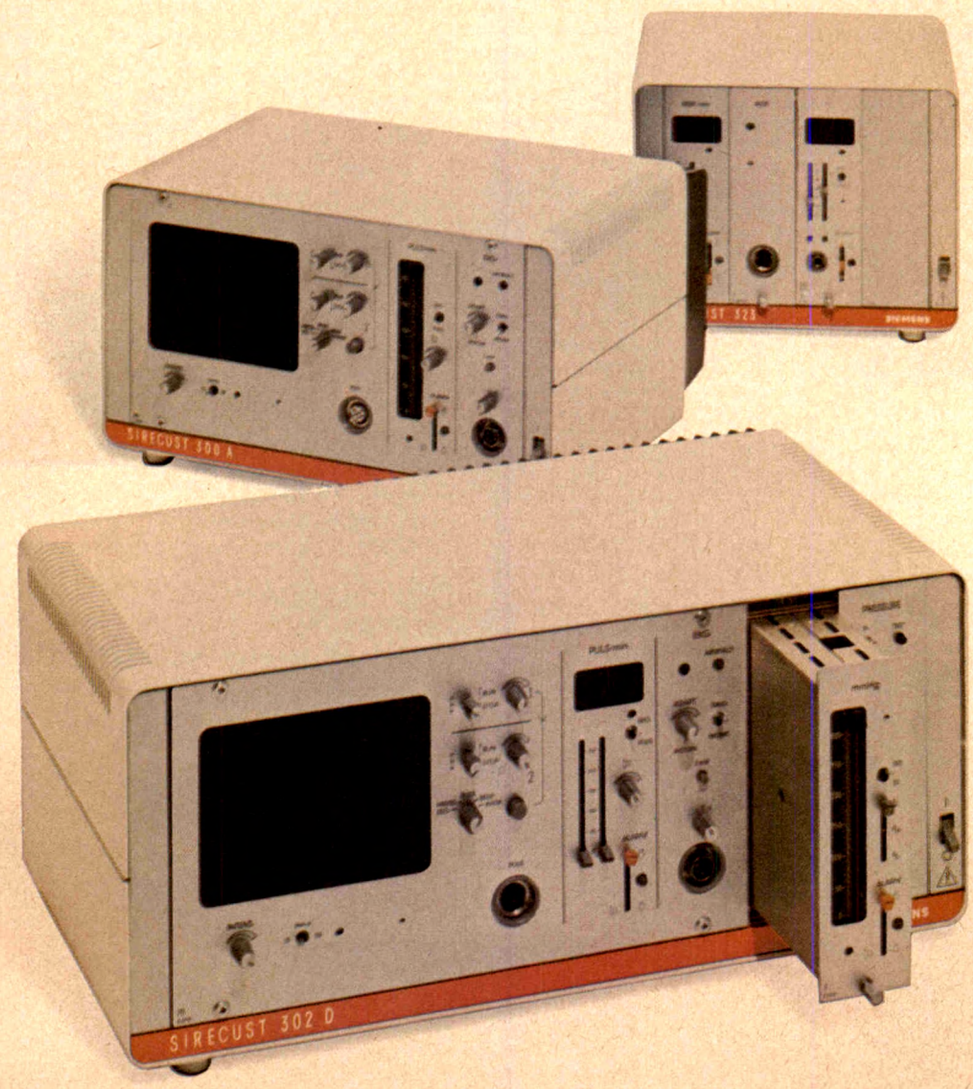
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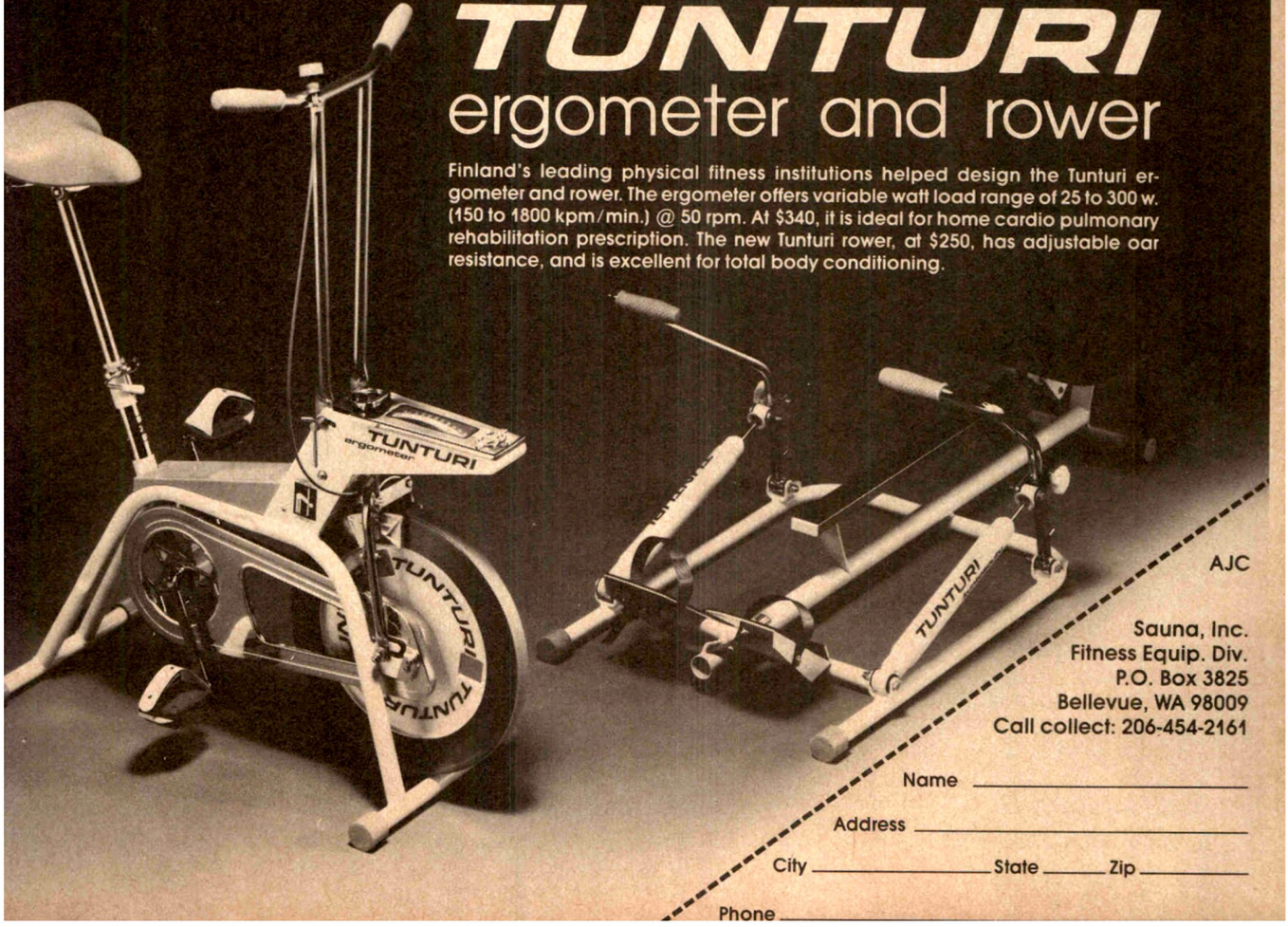
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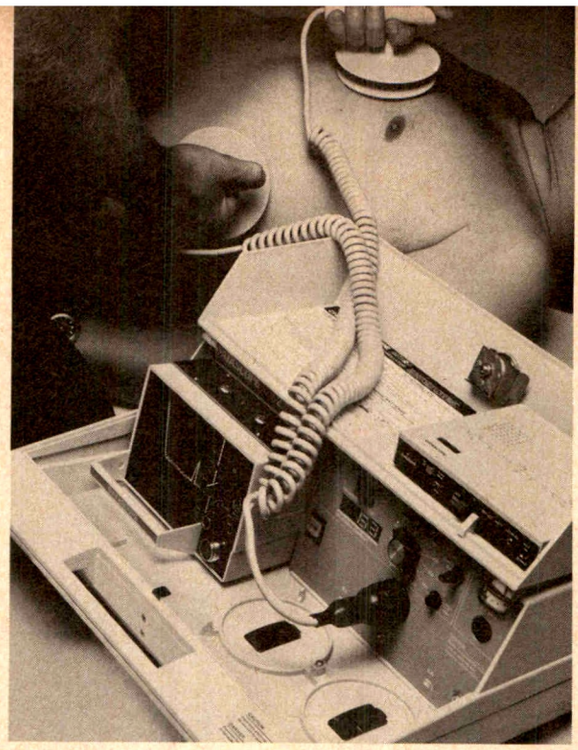
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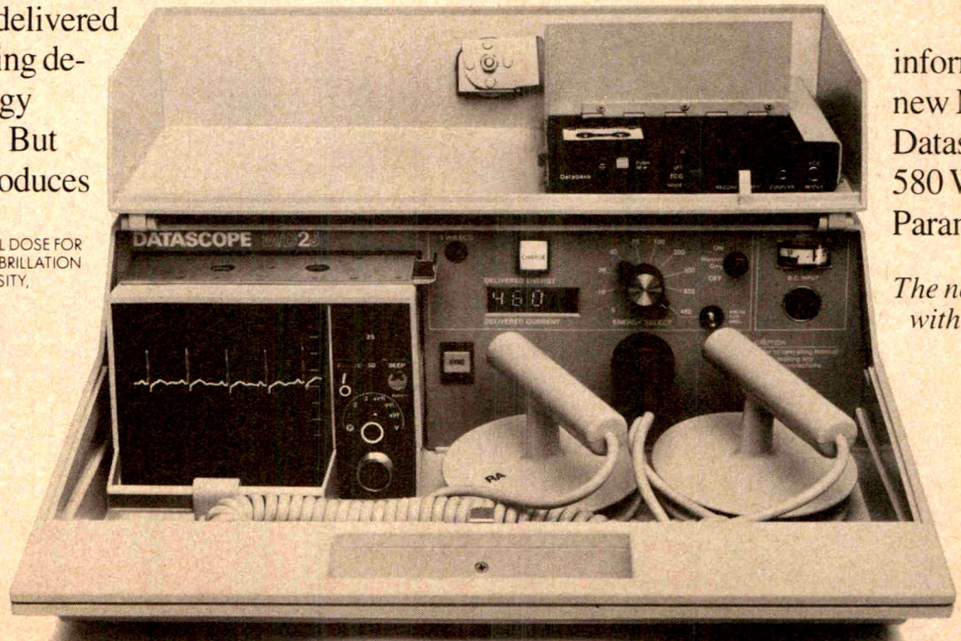
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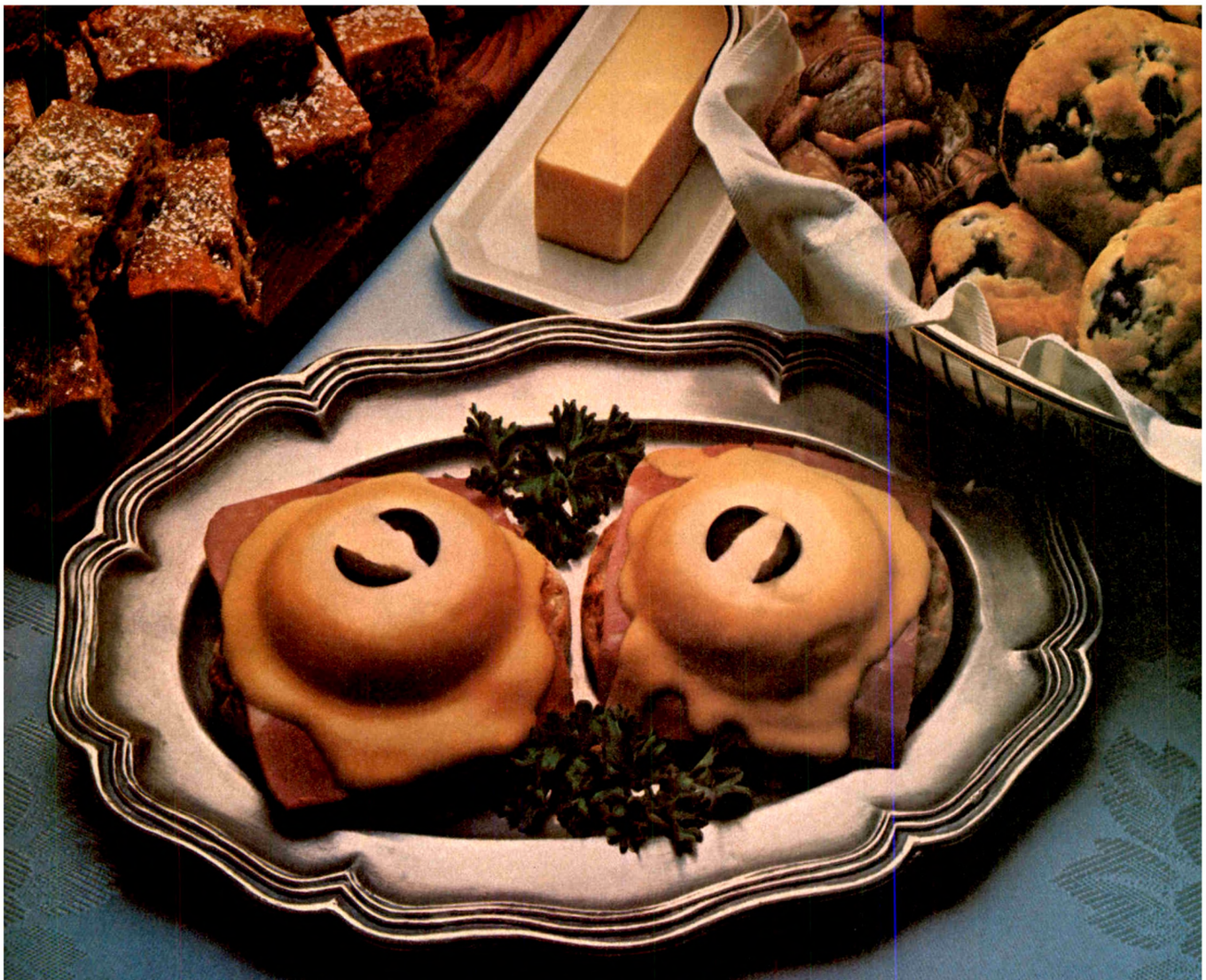
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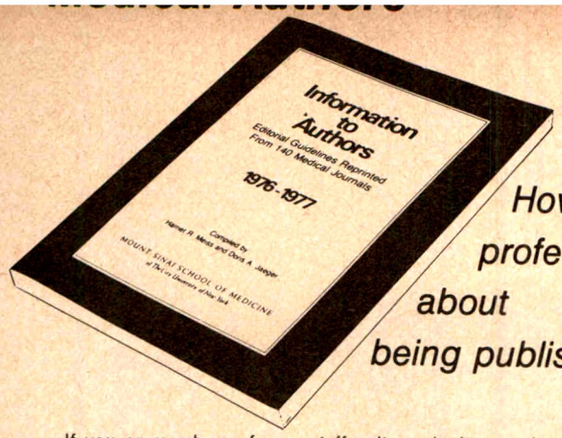
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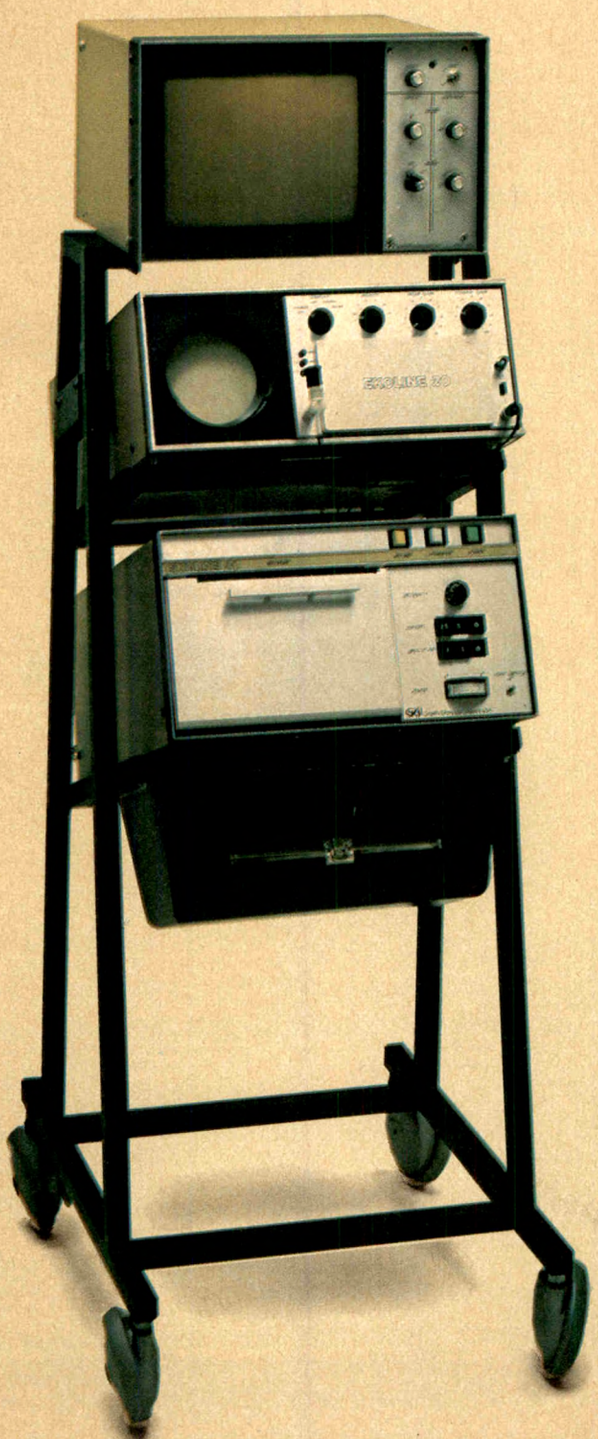
Portable Fiber-optic
Line-Scan Recorder. 1973.

And better.

Large-screen Remote
Monitor. 1974.

And better.

E-21 Recorder. 1976.



And better.

Electrically-isolated
ECG Module. 1973.

And better.

Multi-Parameter
Amplifier Module. 1975.

And better.

Low-cost Switched Gain
Control. 1976.

Innovation without obsolescence.

When we say better, we mean better.

We added no less than six important features to the original Ekoline in its first ten years.

Not bad.

But in the next four years, we added six *additional* capabilities you see listed on the opposite page.

That's terrific. Especially since every one of these innovations protect your original investment in Ekoline 20A while increasing its value to you.

The portable Fiber-optic Line-Scan Recorder produces continuous strip-chart recordings of echo patterns—an especially useful diagnostic aid in a wide variety of cardiac applications.

The Electrically-isolated ECG Module converts the A-mode echo display from a moving organ into a dynamic M-mode display of motion patterns.

The Large-Screen Remote Monitor displays echo information on a 12-inch screen utilizing a high-persistence oscilloscope—a useful accessory when group viewing is required.

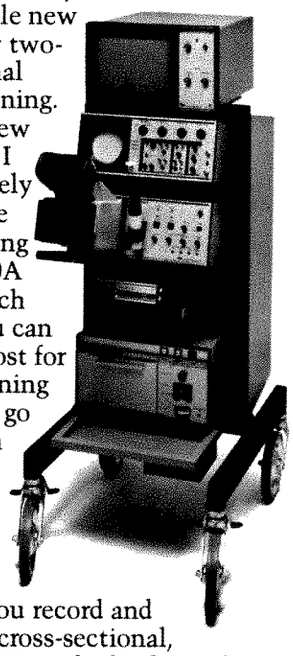
The Multi-Parameter Amplifier Module permits the display of phono and carotid pulse or apex trace information.

The E-21 Recorder utilizes wider paper to permit continuous strip-chart recordings of more parameters than previously possible.

The Switched Gain Control is a low-cost accessory that permits both high gain and low gain information to appear simultaneously on the strip-chart recorder for more accurate diagnosis of difficult-to-see structures.

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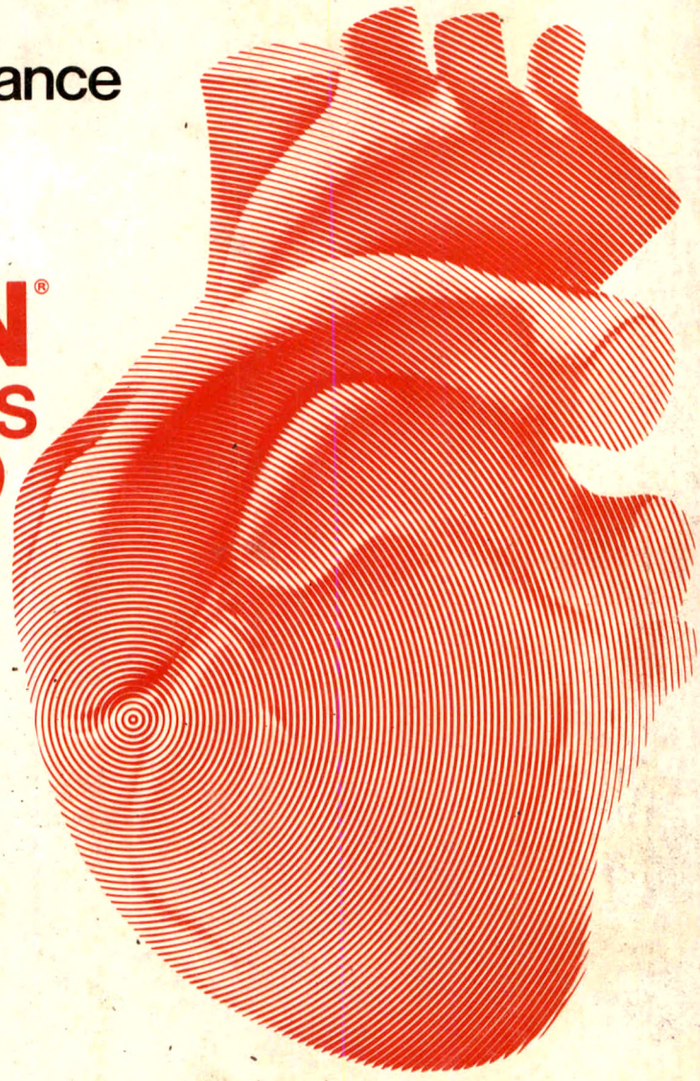
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- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

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SEPTEMBER 1977

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Ventricular Cavity Obliteration Versus Obstructive Cardiomyopathy

Intraaortic Balloon Pump in Surgical and Medical Patients

Review on Cardiac Rupture

Last Call for Abstracts: ACC 27th Annual Scientific Session
Anaheim, California, March 6 to March 9, 1978

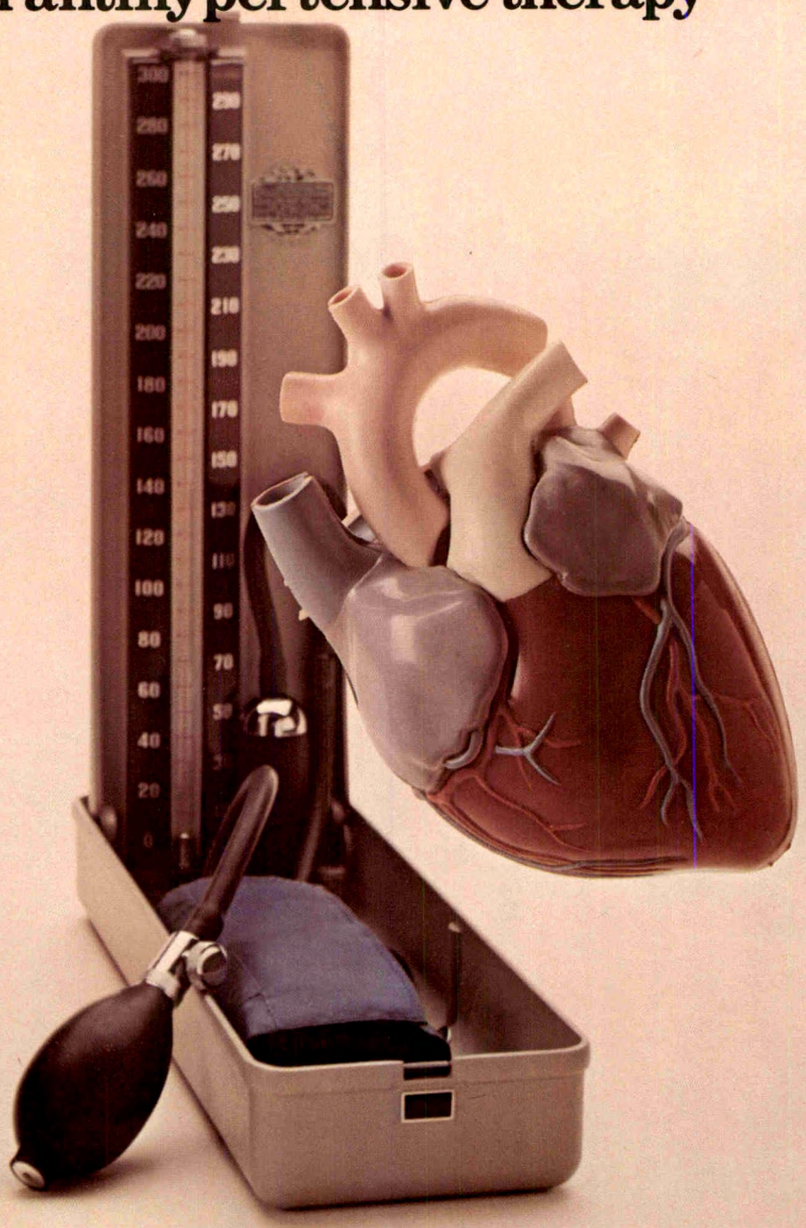
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A Dual Challenge

in antihypertensive therapy



to lower blood pressure effectively...

without compromising existing cardiac output

in hypertension

TABLETS: 250 mg, 500 mg, and 125 mg

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(METHYLDOPA | MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function— cardiac output is usually maintained

ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

MSD
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For a brief summary of prescribing information, please see following page.

addendum

MSD
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Some other characteristics of **ALDOMET** (Methyldopa, MSD) for your consideration

ALDOMET usually lowers blood pressure and:

- Usually does not compromise existing renal function
- Infrequently causes symptomatic postural hypotension
- Normal or elevated plasma renin activity may decrease during the course of therapy
- Usually is well tolerated. Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms. However, significant adverse effects due to ALDOMET have been infrequent. (See brief summary for a complete listing of adverse reactions.)

ALDOMET is useful in all degrees of hypertension and offers dosage flexibility with three tablet strengths—the standard 250 mg, the convenient 500 mg, and the 125 mg.



in hypertension

ALDOMET®
(METHYLDOPA|MSD)

helps lower blood pressure effectively... usually with no direct effect on cardiac function– cardiac output is usually maintained

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third month of therapy; increased dosage or adding a thiazide frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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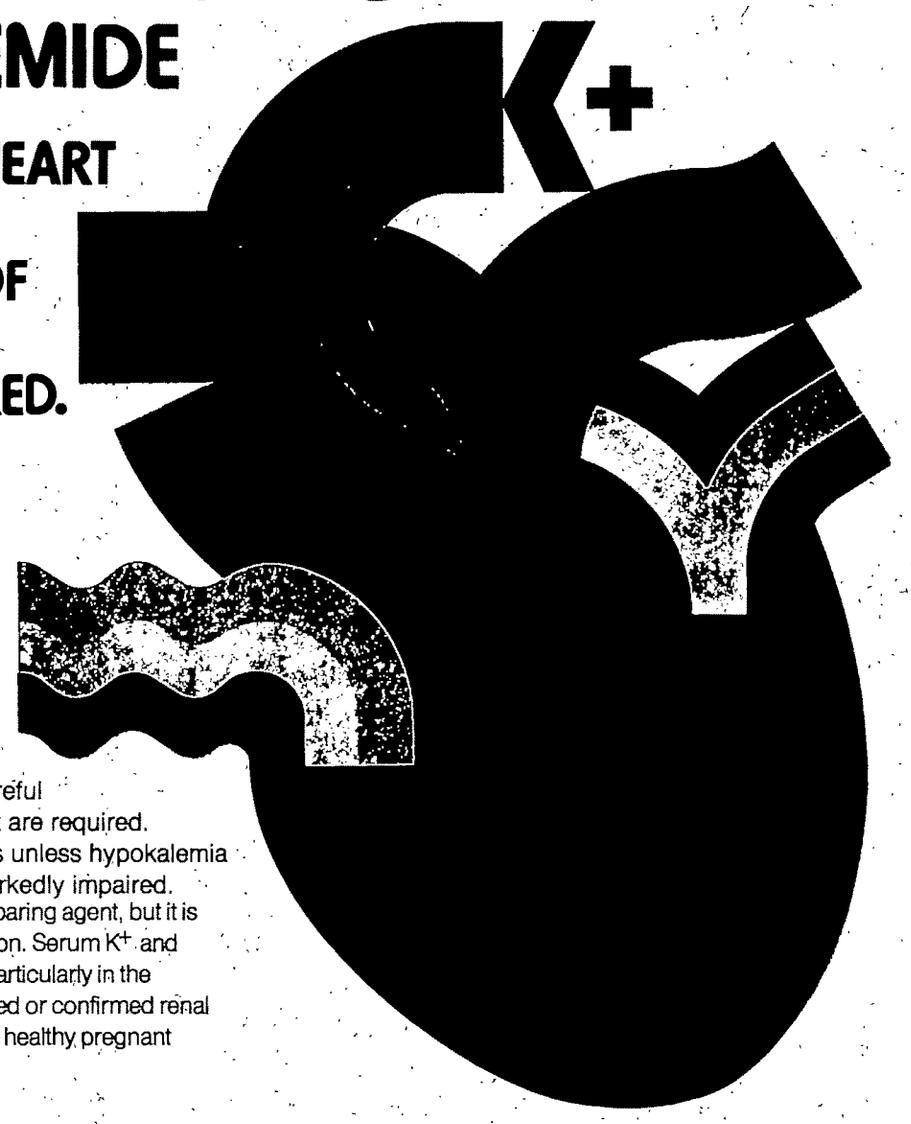
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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis and nephrotic syndrome; steroid induced edema, idiopathic edema, and edema due to secondary hyperaldosteronism, to increase diuresis in patients resistant to other diuretics. Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy when edema is due to pathological causes (see Warnings).

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

Dyrenium and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

SK&F CO. Carolina, P.R. 00630

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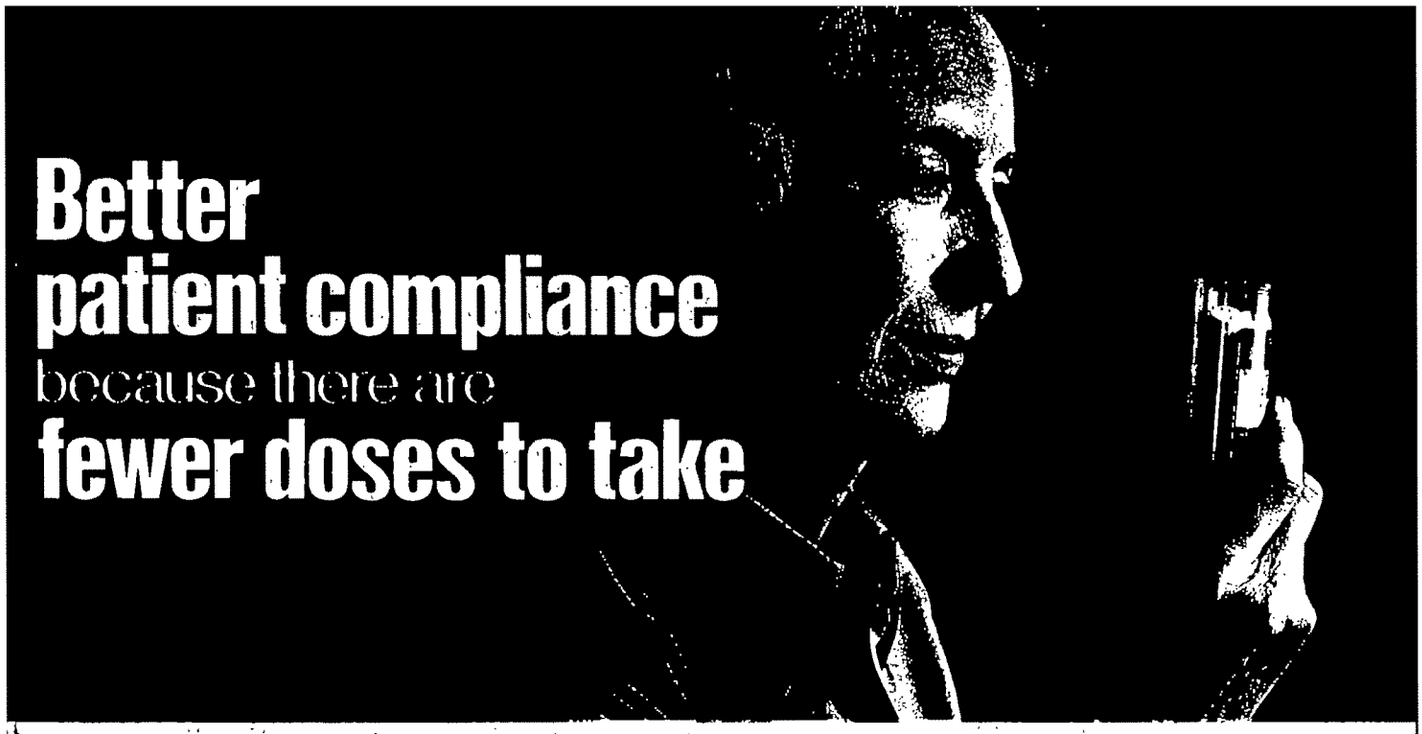
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480 **American College of Cardiology News**

Better patient compliance because there are fewer doses to take



Quinaglute maintains normal sinus rhythm with a convenient 8 or 12 hour dosage schedule.

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Indications:
Premature atrial and ventricular contractions. Paroxysmal atrial tachycardia. Paroxysmal A-V junctional rhythm. Atrial flutter. Paroxysmal atrial fibrillation. Established atrial fibrillation when therapy is appropriate. Paroxysmal ventricular tachycardia when not associated with complete heart block. Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.
NOTE: Depending upon the response desired, the dosage may need to be varied and the blood level and/or electrocardiographic response closely monitored during initial treatment.

Contraindications: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.
Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening. Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects; ventricular premature beats, ventricular tachycardia or flutter while on the drug. Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis. Idiosyncrasy or hypersensitivity to quinidine.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

Precautions: The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.
Quinidine in large doses may reduce the contractile force of the heart; therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication.
It should be administered cautiously, if at all, to senile patients. Hospitalization for close clinical observations, electrocardiographic monitoring, and possibly plasma quinidine levels, is indicated when large doses are used, or with patients who present an increased risk.

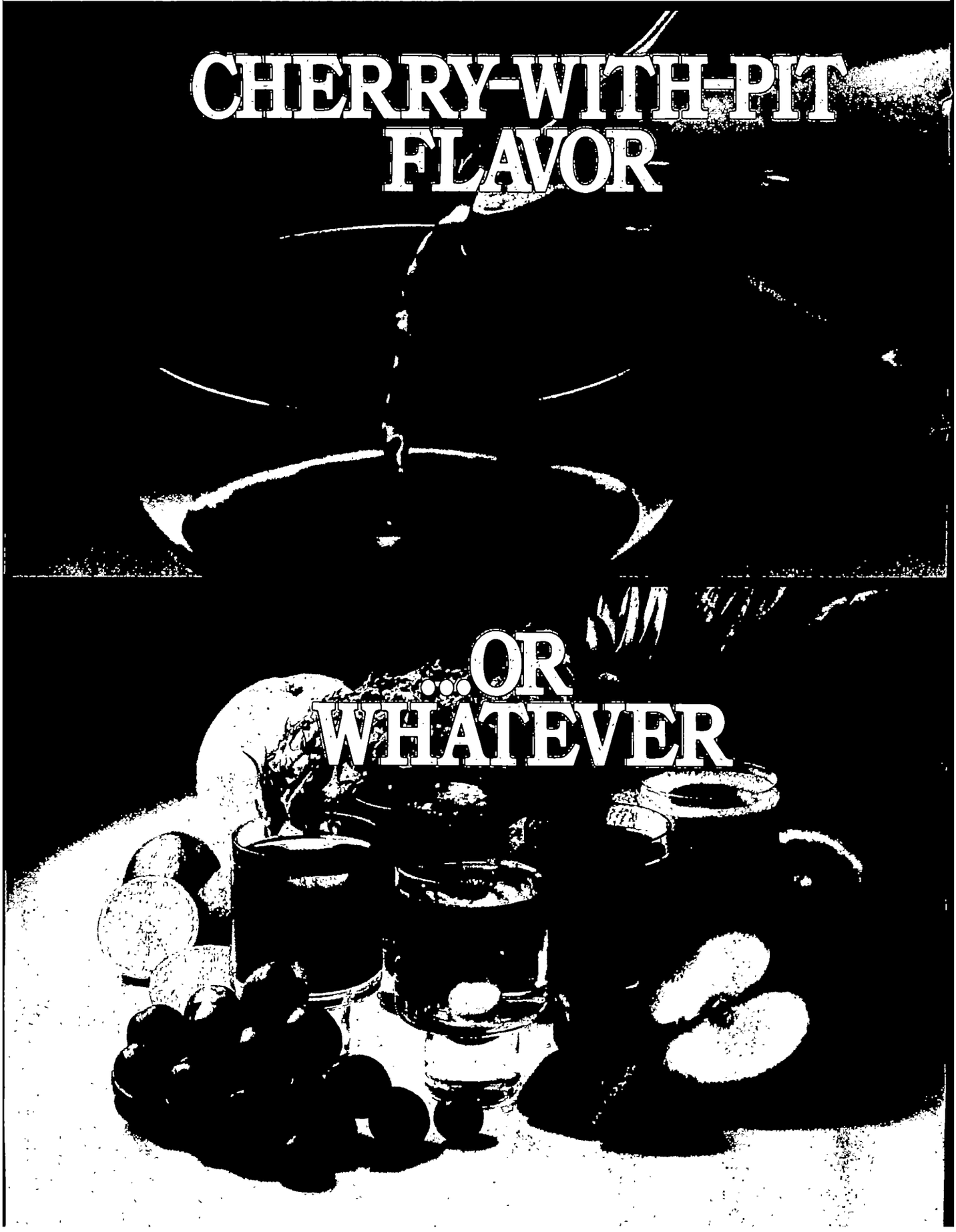
Adverse Reactions: Cinchonism, tinnitus, decreased auditory acuity, vertigo, headache, blurred vision, color perception disturbances, photophobia, diplopia, night blindness, scotomata, reduced visual fields, mydriasis, hypotension, respiratory distress, and gastrointestinal disturbances.

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Convenience in therapeutic doses.
Both forms of KLORVESS offer 20 mEq of potassium and chloride in each dose. There is no need to prescribe several slow-release tablets per dose or space dosage administration beyond the patient's normal routine. Prescribe KLORVESS Liquid or KLORVESS Effervescent Tablets . . . for potassium supplement therapy that offers good taste and convenience at therapeutic dosages.

Description: Klorvess Effervescent Tablets: Each dry, sodium- and sugar-free effervescent tablet contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g. Dissolution of the tablet in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

Indications: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

Contraindications: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

Precautions: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements.

Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis.

High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest.

To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve each Klorvess Effervescent Tablet in 3 to 4 ounces of water or fruit juice, or dilute each tablespoonful of Klorvess (potassium chloride) 10% Liquid in 3 to 4 ounces of water. Both of these solutions should be ingested slowly with or immediately after meals.

Adverse Reactions: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts.

The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest.

The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

Dosage and Administration: Klorvess Effervescent Tablets: Adults—One Klorvess Effervescent Tablet (20 mEq each of potassium and chloride) completely dissolved in 3 to 4 ounces of cold water or fruit juice 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) of Klorvess Liquid (20 mEq of potassium chloride) completely diluted in 3 to 4 ounces of water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating. Deviations from these recommended dosages may be indicated in certain cases of hypokalemia based upon the patient's status. The average total daily dosage must be governed by the patient's response as determined by frequent evaluation of serum electrolytes, EKG and clinical status.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Treatment of Hyperkalemia: 1. Dextrose solution, 10 or 25% containing 10 units of crystalline insulin per 20 g dextrose, given IV in a dose of 300 to 500 ml in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resins, orally and as retention enema. (Caution: Ammonium compounds should not be used in patients with hepatic cirrhosis.) 3. Hemodialysis and peritoneal dialysis. 4. The use of potassium-containing foods or medicaments must be eliminated. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

How Supplied: Klorvess Effervescent Tablets (white)—60 tablets (2 Rx units of 30 effervescent tablets each). Each tablet is individually foil wrapped. Klorvess (potassium chloride) 10% Liquid (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Tablets and Liquid are also available in institutional packaging as follows: Klorvess Tablets—30 and 1000 tablets; Klorvess Liquid—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

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SEPTEMBER 1977

The American Journal of CARDIOLOGY®

VOLUME 40

NUMBER 3

CONTENTS

CLINICAL STUDIES

303 Clinical Correlates of Left Ventricular Cavity Obliteration

ALBERT E. RAIZNER, ROBERT A. CHAHINE, TETSUO ISHIMORI and MAHIR AWDEH

In this study of 24 patients the frequent association of left ventricular cavity obliteration (an angiographic phenomenon in which apical intracavitary space becomes totally occupied in systole by the contracting left ventricular muscle) with hypertension, aortic stenosis and symmetric hypertrophy suggests a pathophysiologic relation to pressure overload. In some patients it may be caused by idiopathic hypertrophic subaortic stenosis. Physical findings include an atrial gallop (92 percent) and a systolic murmur (67 percent). Left ventricular hypertrophy was evident in the electrocardiogram of 71 percent and cardiomegaly in the chest X-ray film of only 29 percent. Such cavity obliteration is a contraction abnormality that may be seen in a spectrum of ventricular hypertrophic disease states. It frequently exhibits hemodynamic phenomena, such as an intraventricular pressure gradient and postextrasystolic beat phenomenon that may be a physiologic consequence of cavity obliteration and not necessarily outflow tract obstruction.

310 Septal Perforator Compression (Narrowing) During Systole in Idiopathic Hypertrophic Subaortic Stenosis

AUGUSTO D. PICHARD, JOSE MELLER, LOUIS E. TEICHHOLZ, STEPHEN LIPNIK, RICHARD GORLIN and MICHAEL V. HERMAN

Coronary arteriography in patients with idiopathic hypertrophic subaortic stenosis demonstrated the presence of previously unreported systolic narrowing (compression) of the septal perforator branches of the left anterior descending coronary artery. The most severe narrowing was found in patients with an intraventricular gradient at rest or severe outflow tract obstruction on provocation with specific interventions such as the Valsalva maneuver or isoproterenol infusion. Such systolic compression of the septal perforator arteries is possibly related to an abnormal position of the septal arteries within the septum in idiopathic hypertrophic subaortic stenosis. It is not necessarily a pathognomonic sign of this anomaly but can occur in any situation under similar physiologic conditions.

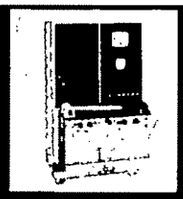
315 Phasic Aortocoronary Bypass Graft Blood Velocity During Ventricular Arrhythmias in Man

ALBERTO BENCHIMOL and KENNETH B. DESSER

These Doppler flowmeter studies in 16 patients show that ventricular arrhythmias adversely influence aortocoronary bypass graft function and support aggressive treatment of ventricular arrhythmias in subjects with such grafts. Ventricular extrasystoles reduced peak systolic and diastolic graft blood velocities by 20 to 80 percent; coupled salvos caused diastolic bypass blood velocity to cease; and ventricular tachycardia produced an average 50 percent decrease in peak graft blood velocity. In 14 of the 16 subjects termination of the tachycardia was associated with a marked "overshoot" of peak systolic and diastolic blood velocities during the first three to eight succeeding sinus beats. This increase probably represents a form of postextrasystolic potentiation similar to blood velocity profiles at other anatomic sites after these arrhythmias.

Continued on page A14

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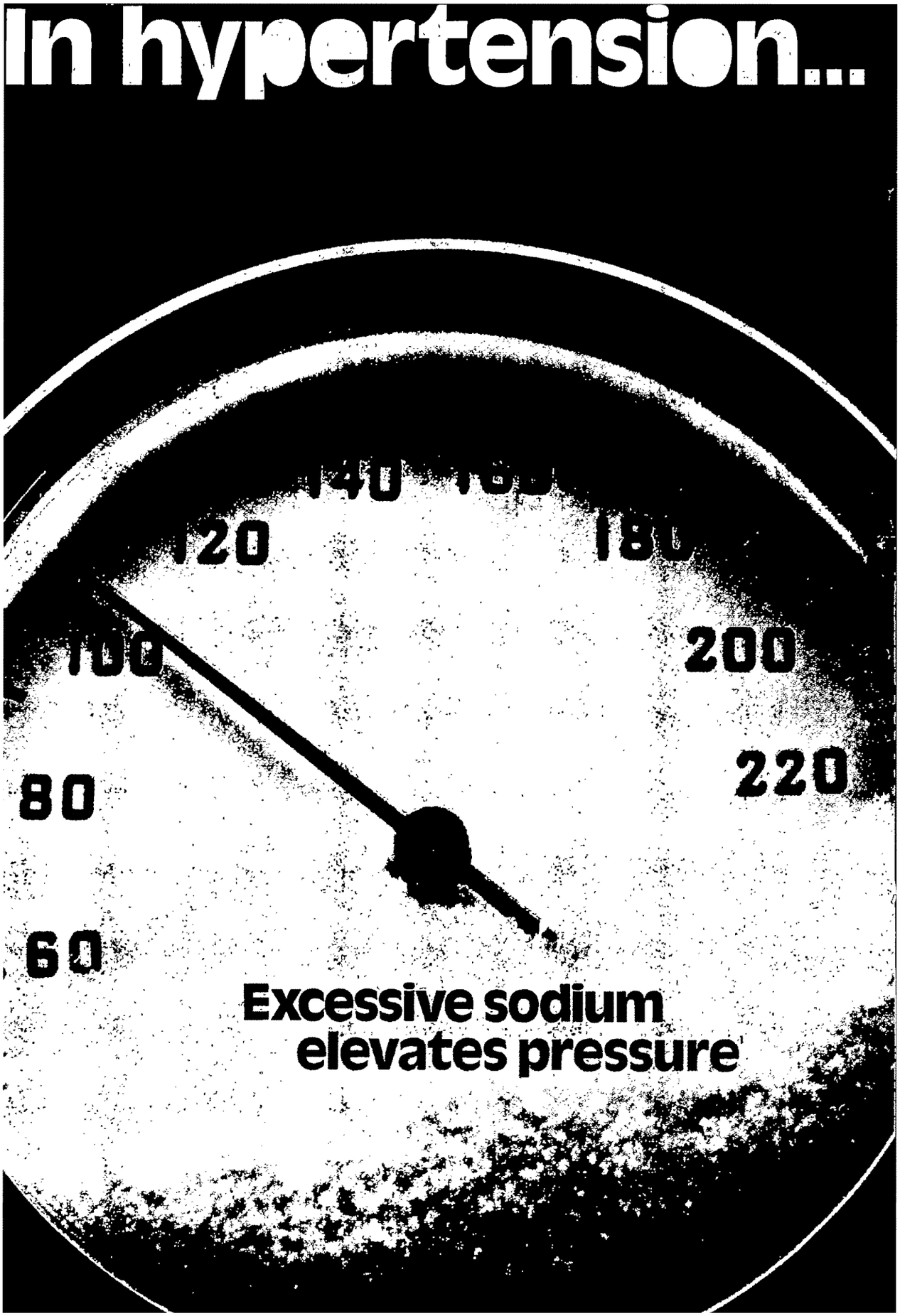
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Diuretics reduce blood pressure by blocking sodium retention to lower "effective" volume. But, the body's renal compensatory mechanisms are mobilized to promote sodium conservation, expand "effective" volume and reelevate blood pressure. Sustained control of "effective" volume is therefore essential to treatment. Hygroton blocks sodium retention longer than any other diuretic available.

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Reduced blood pressure resulting from the use of step-2 agents (reserpine, methyldopa, propranolol) may cause compensatory sodium retention, secondary volume expansion and, eventually, reelevation of blood pressure. For this reason, the National Task Force[2] recommends the use of diuretics as baseline agents with step-2 therapy. Hygroton is an "ideal" choice because of its sustained blockade of sodium retention, dosage simplicity and enhanced patient compliance.

Hygroton® 50 mg.
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Provides smooth, sustained control

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema.

Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance.

Adverse Reactions: Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.

Usual Dose: One tablet daily.

How Supplied: Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

References:

1. Laragh, J.H. et al.: Vasoconstriction - volume analysis for understanding and treating hypertension. The use of renin and aldosterone profiles, in Hypertension Manual (Laragh, J.H., ed.). New York, Dun-Donnelley, 1974, pp. 824-825. **2.** Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: A Cooperative Study, JAMA 237:255, January 17, 1977.

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CONTENTS

319 **Structural Changes in Porcine Xenografts Used as Substitute Cardiac Valves. Gross and Histologic Observations in 51 Glutaraldehyde-Preserved Hancock Valves in 41 Patients**

THOMAS L. SPRAY and WILLIAM C. ROBERTS

Gross changes in 51 Hancock glutaraldehyde-preserved porcine heterograft bioprostheses included thrombosis (5 prostheses) and degeneration (3 prostheses) of the cusps. Major histologic changes in 44 bioprostheses included fibrin deposits, inflammatory cell infiltrates, histiocyte deposition, giant cell formation and focal disruption of the fibrocollagenous structure of the cusps. These results indicate that porcine bioprostheses are not biologically inert in the human circulation, but that valve failure is rare, at least as manifested within the 75 month observation period of this study. The Hancock stabilized glutaraldehyde preservation technique creates more stable cross-linking of collagen and less tissue antigenicity than formalin fixation. No clear evidence of valve-related thromboemboli was found. In this study prosthetic dysfunction usually occurred as a result of technical factors.

331 **Pathologic Findings After Cardiac Valve Replacement With Glutaraldehyde-Fixed Porcine Valves**

MICHAEL C. FISHBEIN, SALLY A. GISSEN, JOHN J. COLLINS, Jr., ERNEST M. BARSAMIAN and LAWRENCE H. COHN

Of 311 patients in this series, 7 percent died intraoperatively or less than 1 month after glutaraldehyde-fixed porcine valve replacement, generally from clinical cardiovascular deterioration resulting from severe coronary arterial arteriosclerosis, hemorrhagic myocardial necrosis, pulmonary disease or postoperative hemorrhage rather than from pathologic processes affecting the implanted valve. On the other hand, clinical cardiovascular deterioration in the late postoperative period was more often related to infection, thrombosis or degeneration affecting the implanted valve. Advantages of the glutaraldehyde-fixed porcine valve include the rarity of prosthetic disproportion and thromboembolic complications. Anticoagulation therapy is usually unnecessary when this type of valve is implanted. Collagen degeneration, a well known complication of other tissue valves, affected only one valve in this series.

338 **Clinical Experience With the Smeloff-Cutter Aortic Valve Prosthesis: An 8-Year Follow-Up Study**

RADHA SARMA, E. JOHN ROSCHKE, EARL C. HARRISON, W. ALLAN EDMISTON and FRANCIS Y. K. LAU

Favorable follow-up results in 46 survivors of aortic valve replacement with the present model Smeloff-Cutter prosthesis between 1968 and 1973 indicate that this prosthesis deserves serious consideration when a rigid prosthesis for aortic valve replacement is contemplated. This prosthesis produced a considerable reduction in pressure across the aortic valve and a significant prolongation of left ventricular ejection time. Functional improvement was noted in 33 of the 38 current survivors. All patients in this series were receiving anticoagulant drugs. Two patients had pulmonary emboli and one a bland embolus to a systemic artery. No ball variance or other type of material failure occurred. During this 8 year period of observation there were eight deaths and an increased incidence of gallstones.

345 **Thirteen Year Experience With Aortic Valve Replacement**

JOSEPH W. RUBIN, H. VICTOR MOORE, RAYMOND F. HILLSON and ROBERT G. ELLISON

This report on the long-term examination of 241 consecutive patients subjected to isolated aortic valve replacement at the Medical College of Georgia between 1963 and 1976 provides clinically useful information on prosthesis-related survival rates, complications, rehabilitation and late clinical characteristics of six valve types. These data show that longevity and rehabilitation are related to replacement of the aortic valve before the onset of severe myocardial decompensation and to meticulous management to avoid lethal complications inherent

Continued on page A17

N PREDICTABLE ANGINA*



...during episodes of emotional stress

MMARY OF PRESCRIBING INFORMATION

ndications: Based on a review of this drug by The National Academy f Sciences—National Research Council and/or other information, DA has classified the indications as follows:

Probably effective: The marketed dosage form of SORBITRATE s indicated for the treatment of acute coronary attacks and/or prophylaxis in situations likely to precipitate such attacks.

Final classification of the less than effective indications requires rther investigation.

ntraindications: A history of sensitivity to the drug.

rnings: Data supporting the use of nitrates during the early days of the ute phase of myocardial infarction are insufficient to establish safety.

ecautions: Tolerance develops to the nitrates and cross tolerance with other nitrates may occur.

verse Reactions: Headache which may be severe and persistent. Usually ng the dose and using analgesics will help control. If headaches which ually diminish or disappear as therapy is continued.

Allergic reactions seen occasionally: Dizziness, vertigo, flushing, weakness, transient dizziness and weakness as well as other signs of cerebral emia associated with postural hypotension. Individuals at risk from l to the hypotensive effects of nitrates should be observed closely for cur even with the usual therapeutic dose for the first few doses. Exfoliative drug rash and fixed erythematous dermatitis.

Flushing can also be physiological and nonsensitive, but may also be related to histamine and other agents.

sage and Administration: *Individualize dosage to maximize increase in exercise tolerance* which may occur optimally at doses titrated with chewable tablets as low as 5 mg, the smallest effective dose of the drug available. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose as necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary vasodilators may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE:

Onset of Effect: 2 to 5 minutes

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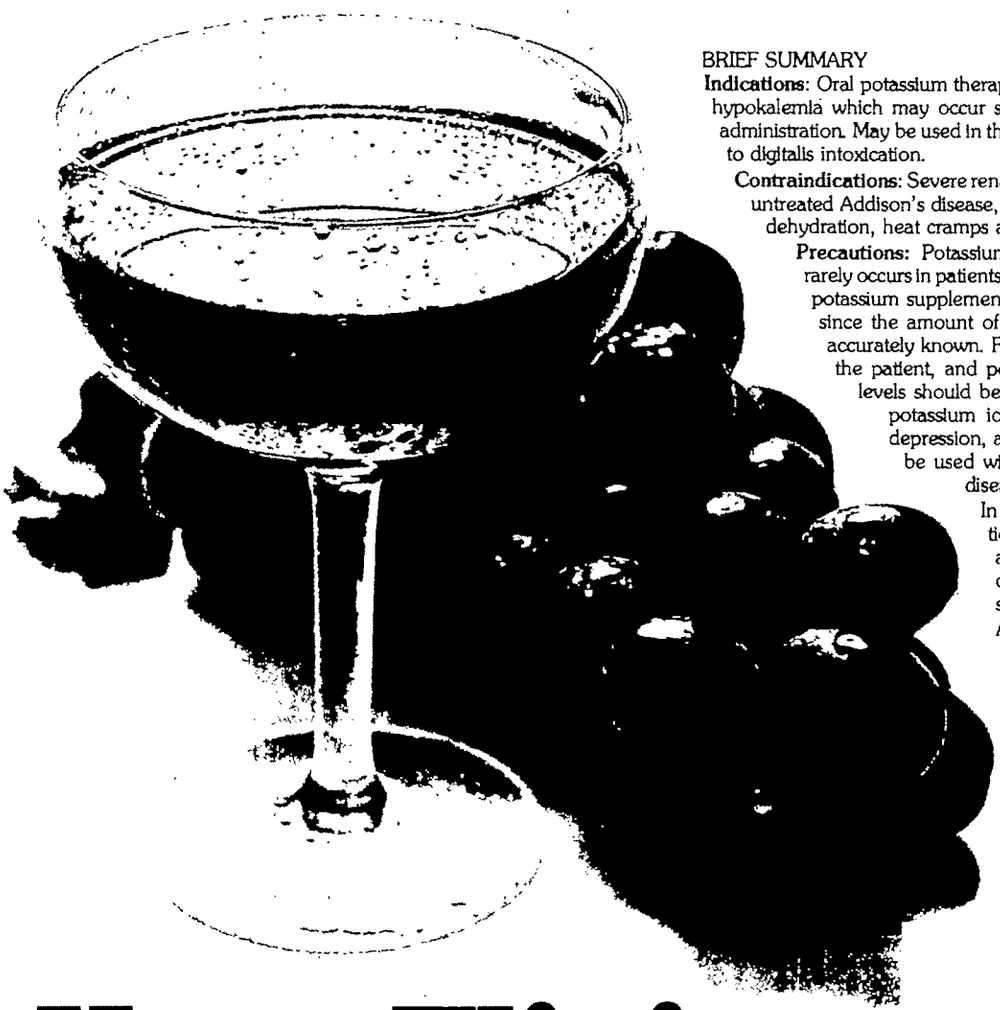
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BRIEF SUMMARY

Indications: Oral potassium therapy for the prevention and treatment of hypokalemia which may occur secondary to diuretic or corticosteroid administration. May be used in the treatment of cardiac arrhythmias due to digitalis intoxication.

Contraindications: Severe renal impairment with oliguria or azotemia, untreated Addison's disease, adynamia episodica hereditaria, acute dehydration, heat cramps and hyperkalemia from any cause.

Precautions: Potassium intoxication by oral administration rarely occurs in patients with normal kidney function, however, potassium supplements must be administered with caution, since the amount of the deficiency or daily dosage is not accurately known. Frequent checks of the clinical status of the patient, and periodic ECG and/or serum potassium levels should be made. High serum concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. This drug should be used with caution in the presence of cardiac disease.

In hypokalemic states, especially in patients on a low-salt diet, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The most severe adverse effect is hyperkalemia.

Overdosage: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications". Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

Kaon® Elixir
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in the individual prostheses. Indications for surgery in aortic valve disease are clearer for aortic stenosis than for aortic regurgitation. The average survival time of 1 1/2 to 3 years for patients with syncope, angina and degrees of left heart failure due to aortic stenosis is a compelling reason for valve replacement. This study showed a 66 percent survival rate in 13 years in the patients with aortic stenosis. If valve replacement can be offered before the development of congestive heart failure in patients with aortic regurgitation, survival and rehabilitation can be improved significantly.

355 **Muscle Fiber Disarray in Common Heart Diseases**

JOHANNA VAN DER BEL-KAHN

A mild degree (less than 5 percent) of myocardial fiber disarray was found at autopsy in 33 patients with such common cardiovascular conditions as systemic hypertension, coronary heart disease or cor pulmonale and in 20 patients with a normal heart. Three types of myocardial fiber deviation included a y-shaped (type I), a fascicular (type II) and a more disorganized (type III) arrangement. Fibrosis most frequently accompanied types I and III muscle fiber arrangements but was often absent or present without any change in normal parallel muscle fiber arrangements. The amount of disarray was considerably less than in patients with hypertrophic cardiomyopathy and its functional impact depends on its location, distribution and quantity.

365 **Effect of Heparin-Induced Free Fatty Acid Elevation on Myocardial Oxygen Consumption in Man**

WILLIAM J. ROGERS, HUEY G. McDANIEL, ROGER E. MORASKI, CHARLES E. RACKLEY and RICHARD O. RUSSELL, Jr.

Metabolic studies in 17 patients with a clinical history suggestive of ischemic heart disease but stable condition showed that acute elevation of plasma free fatty acids to pathophysiologic levels after heparin-induced lipolysis exerted no measurable effect on myocardial oxygen consumption, probably because the excess free fatty acids are stored as triglycerides rather than oxidized. Hemodynamic variables, including mean aortic pressure, heart rate, coronary sinus blood flow and coronary vascular resistance, were unchanged. It is not known if these findings in patients in stable condition can be extrapolated to patients with unstable ischemic heart disease. There is evidence that elevated free fatty acid levels associated with acute myocardial infarction can be reduced by administration of nicotinic acid derivatives, high carbohydrate feedings and glucose-insulin-potassium infusions.

EXPERIMENTAL STUDIES

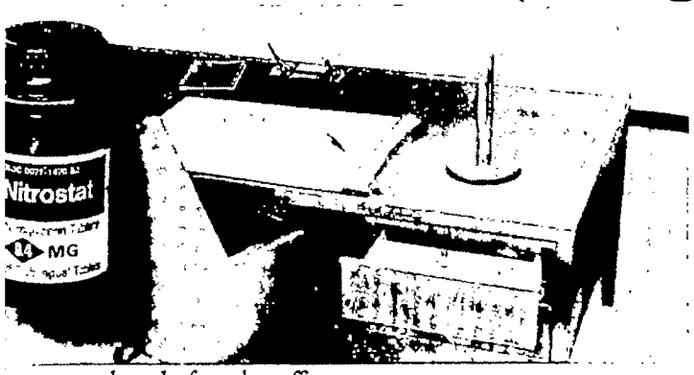
373 **Significance of Subendocardial S-T Segment Elevation Caused by Coronary Stenosis in the Dog. Epicardial S-T Segment Depression, Local Ischemia and Subsequent Necrosis**

ROBERT A. GUYTON, JAMES H. McCLENATHAN, GLENN E. NEWMAN and LAWRENCE L. MICHAELIS

The experimental model in this study in which subendocardial electrograms are used to detect ischemia produced by graded coronary hypotension provides a wide spectrum of experimental states within which conditions similar to those in man may be found. This study of graded coronary stenosis in dogs emphasizes that regional vulnerability to limitation of coronary inflow is heterogeneous although regional coronary blood flow is normally homogeneous. Subendocardial blood flow may be reduced to 25 percent of normal by coronary stenosis and tachycardia while subepicardial flow remains normal, indicating remarkably effective autoregulation of epicardial blood flow concomitant with progressive subendocardial ischemia. A fixed proximal coronary stenosis allows the subepicardium to "steal" perfusion from the subendocardium. This steal effect is greatest over the range of distal coronary pressures in which dilatory reserve persists in the subepicardium but is depleted in the subendocardium. Under the hemodynamic conditions in this study, this range is 40 to 70 mm Hg.

Continued on page A19

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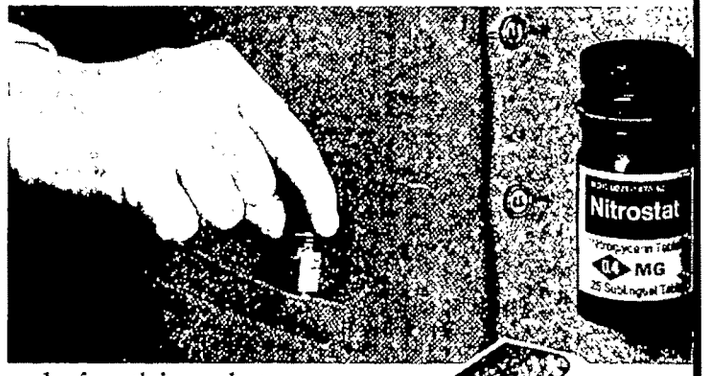
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381 **Evolution of Regional Ischemia Distal to a Proximal Coronary Stenosis: Self-Propagation of Ischemia**

ROBERT A. GUYTON, JAMES H. McCLENATHAN and LAWRENCE L. MICHAELIS

These experiments in open chest dogs at constant preload, afterload and heart rate indicate two positive feedback mechanisms are the means by which ischemia is self-propagating. One is an ischemia-mediated increase in resistance. In these animals local vascular resistance doubled in the most ischemic area of myocardium. The other is a coronary steal mechanism as shown by the reciprocal relation between changes in flow in the left anterior descending coronary artery and changes in collateral flow to the region of the circumflex artery. Although these two mechanisms appear to be operative in these dogs, their functional significance in human infarction is difficult to estimate. However, there is evidence that in man vicious cycles of ischemia causing more ischemia may be initiated by a temporary increase in oxygen demand in the presence of a severe but stable limitation of oxygen supply.

PEDIATRIC CARDIOLOGY

393 **Wenckebach Atrioventricular Block (Mobitz Type I) in Children and Adolescents**

DENNISON YOUNG, ROBERT EISENBERG, BERNARD FISH and JOHN D. FISHER

This provocative study, documenting the development of fixed complete heart block in 7 of 16 (44 percent) of children and adolescents with Wenckebach atrioventricular block (Mobitz type I), is at odds with the concept that Wenckebach periodicity is purely "functional" and of little consequence. Physiologic data, including bundle of His recordings, in athletes also cast significant doubt that a nonorganic functional vagal effect of training is the etiologic factor in these subjects. Because all patients in this series are alive and histologic data are unavailable, it is not known if their altered membrane potential results from a functional disturbance of neurohumoral or other chemical imbalance or from anatomic abnormality due to developmental, inflammatory or degenerative progressive involvement of the conduction system.

400 **Cross-Sectional Echocardiographic Features of Ebstein's Anomaly of the Tricuspid Valve**

MICHAEL J. HIRSCHKLAU, DAVID J. SAHN, ARTHUR D. HAGAN, DAVID E. WILLIAMS and WILLIAM F. FRIEDMAN

Cross-sectional echocardiography in 10 patients provided distinctive diagnostic findings specific for Ebstein's anomaly of the tricuspid valve and was useful in accurately diagnosing this condition. These features included inferior and leftward displacement of the tricuspid valve (nine patients), multiple echoes from the tricuspid valve and elongated tricuspid valve leaflets (seven patients), thickened tricuspid valve leaflets (six patients), excessive excursion of the tricuspid valve (five patients) and "whipping" motion of the valve (three patients). Unlike other reports, this study considered increased right ventricular dimension and systolic anterior septal motion, found in nine subjects, nonspecific features.

405 **Atrial Defect Size After Blalock-Hanlon Atrioseptectomy**

EDWARD B. CLARK, LAUREN J. SWEENEY and GLENN C. ROSENQUIST

Review of 14 heart specimens with transposition of the great arteries and Blalock-Hanlon septectomy in the cardiac pathology collection at the Johns Hopkins Hospital shows that particular attention should be paid to excision of the limbus of the fossa ovalis when closed atrial septectomy is done. Inclusion of the limbus in the surgical specimen produces a larger atrial communication and optimizes bidirectional intraatrial mixing. This larger percent communication may be the result of loss of structural integrity of the foramen portion of the septum so that the communication enlarges further as the atria with their septum enlarge with somatic growth. The largest percent communication was found in a specimen without a limbus excision in which there was a naturally occurring ostium secundum atrial septal defect.

Continued on page A21

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CONTENTS

REPORTS ON THERAPY

409 **Intravenous Diazoxide Therapy in Hypertensive Crisis**

WALTER J. McDONALD, GORDON SMITH, JAMES W. WOODS, H. MITCHELL PERRY and BYRON D. DANIELSON

This multicenter study of 41 severely hypertensive patients treated during hypertensive crises with intravenously administered diazoxide demonstrates the effectiveness, safety and rapidity of action of this drug in reducing blood pressure. Diastolic blood pressure was reduced from an average of 139 to 98 mm Hg within 10 minutes. Therapy was judged effective in 38 of 41 patients, although 35 percent of injections were ineffective. The concomitant administration of furosemide had no additional beneficial antihypertensive effect. Nine percent of patients had side effects that were transient and relatively innocuous. No significant changes in mean blood urea nitrogen or electrocardiograms were noted 2 weeks after diazoxide therapy. No patient showed clinical evidence of diazoxide-induced deterioration of the coronary circulation.

416 **Results and Complications of Intraaortic Balloon Pumping in Surgical and Medical Patients**

ARMAND A. LEFEMINE, BERNARD KOSOWSKY, IRVING MADOFF, HARRISON BLACK and MARY LEWIS

Intraaortic balloon pumping providing significant assistance to the heart and circulation of surgical and medical patients with shock, low cardiac output, left ventricular dysfunction or impending myocardial infarction proved technically feasible with various degrees of success in 86 of 94 subjects. Ten of the 14 patients with cardiogenic shock survived—an unusually high survival rate of 71 percent. The results in surgical patients failing to tolerate removal of pump-oxygenator support at the end of their cardiac procedure were similar to those of other reports. Complications ranging from mild to severe developed in 17 percent of the entire group of 86 patients and in 50 percent of the medical patients with cardiogenic shock. These were usually the result of diseased arteries, low cardiac output and the limitations of current technology. Arterial insufficiency requiring removal of the balloon was the most common complication.

421 **Acute Effects of Glucose-Insulin-Potassium Infusion on Myocardial Substrates, Coronary Blood Flow and Oxygen Consumption in Man**

WILLIAM J. ROGERS, RICHARD O. RUSSELL, Jr., HUEY G. McDANIEL and CHARLES E. RACKLEY

Glucose-insulin-potassium infusion in 13 fasting men with a clinical history suggestive of ischemic heart disease caused prompt alteration in myocardial substrate utilization from lipid to carbohydrate, a measurable increase (12 percent) in coronary sinus blood flow and a 13 percent decrease in coronary vascular resistance, a small significant increase in serum osmolarity but no significant measurable change in myocardial oxygen consumption. The alteration in coronary sinus blood flow is a consequence of reduced coronary resistance that may be related to the small acute increase in serum osmolarity. These results cannot be immediately extrapolated to acutely ischemic hearts without further investigation. If glucose-insulin-potassium infusion is clinically useful in salvaging an ischemic myocardium, the mechanism is probably not related to decreased myocardial oxygen consumption secondary to the shift from lipid to carbohydrate metabolism.

REVIEWS

429 **Cardiac Rupture—Challenge in Diagnosis and Management**

ROBERT J. BATES, STEVEN BEUTLER, LEON RESNEKOV and C. E. ANAGNOSTOPOULOS

Rupture of the heart causes death in more than 25,000 persons a year in the United States. Free transmural rupture occurs in up to 24 percent of fatal acute myocardial infarctions and, after cardiogenic shock and dysrhythmias, is the most important cause of sudden death after myocardial infarction. In this series of 20 cases rupture occurred within 4 days in 50 percent and within 14 days in 87 percent. More than 90 percent of cardiac ruptures

Continued on page A23

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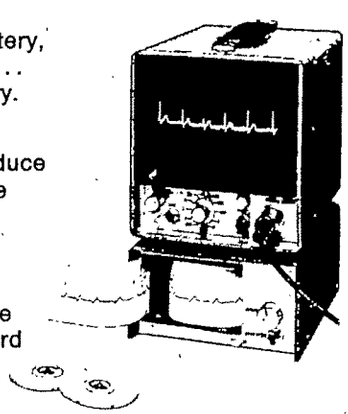
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occur through the left ventricle. Age is a significant unfavorable risk factor for cardiac rupture. Although there is no single diagnostic electrocardiographic characteristic of impending cardiac rupture, the sudden appearance of tall T waves in the precordial leads or the development of a monophasic RS complex with an upright T wave and progressive S-T segment elevation have been reported just before rupture. Therapeutic attempts have not been very successful.

DIAGNOSTIC SHELF

438 Loeffler's Endocarditis Presenting as Mitral and Tricuspid Stenosis

ARTHUR E. WEYMAN, ROBERT RANKIN and HAROLD KING

The unusual combination of mitral and tricuspid stenosis in a 35 year old woman with Loeffler's endocarditis required surgical intervention. Mitral valve replacement and limited tricuspid valvulotomy were successfully performed with marked alleviation of symptoms and no evidence of aggravation of the endocarditis. In addition to the valve lesions microscopic sections of the endocardium and fragments of myocardium showed pronounced fibrous thickening of the endocardial layer. Postoperative serial echocardiograms demonstrated normal left ventricular function with a normally functioning mitral valve prosthesis. The pulmonary valve echogram also returned to normal. This case demonstrates the feasibility of surgical intervention in patients with Loeffler's endocarditis whose valve disease represents the primary derangement.

445 Displacement of the Heart by a Giant Mediastinal Cyst

PAUL C. KOCH, ITZHAK KRONZON, HOWARD E. WINER, PETER ADAMS and MAX TRUBEK

This case report illustrates the valuable diagnostic role of echocardiography in clarifying the actual location and normalcy of the displaced heart and the cystic nature of the mass that shifted it in a 57 year old woman with chest discomfort, dyspnea on exertion, ankle edema of 1 year's duration and a precordial systolic thrill and murmur. After thoracotomy when a large anterior mediastinal benign fibrous cyst with organized hemorrhage was removed, the heart gradually returned to a more normal position, the patient's symptoms were completely relieved and her thrill and murmur vanished. This case was remarkable because the heart was displaced into the right upper quadrant of the chest and the cyst could not be easily differentiated in the chest roentgenogram from a normally located but enlarged heart.

449 Echocardiographic Study of Malfunction of the Bjork-Shiley Prosthetic Heart Valve in the Mitral Position

JOSE ALBERTO BERNAL-RAMIREZ and JOHN H. PHILLIPS

The echocardiographic functional assessment of the Bjork-Shiley prosthetic valve in the mitral valve position is complicated by the spatial asymmetry of the tilting disc. The normal postoperative pattern with this valve shows paradoxical septal motion. In this study two distinctive echocardiographic motion patterns proved helpful in detecting malformation of a Bjork-Shiley prosthetic mitral valve in four patients. A rounded slowed pattern of opening and closure correlated with the presence of abnormal clotting on the prosthesis in two patients. A second pattern showing an unusual "hump" during the opening phase correlated with a significant perivalve leak in two subjects. Corrective surgery in three patients restored normal motion of the prosthetic valve.

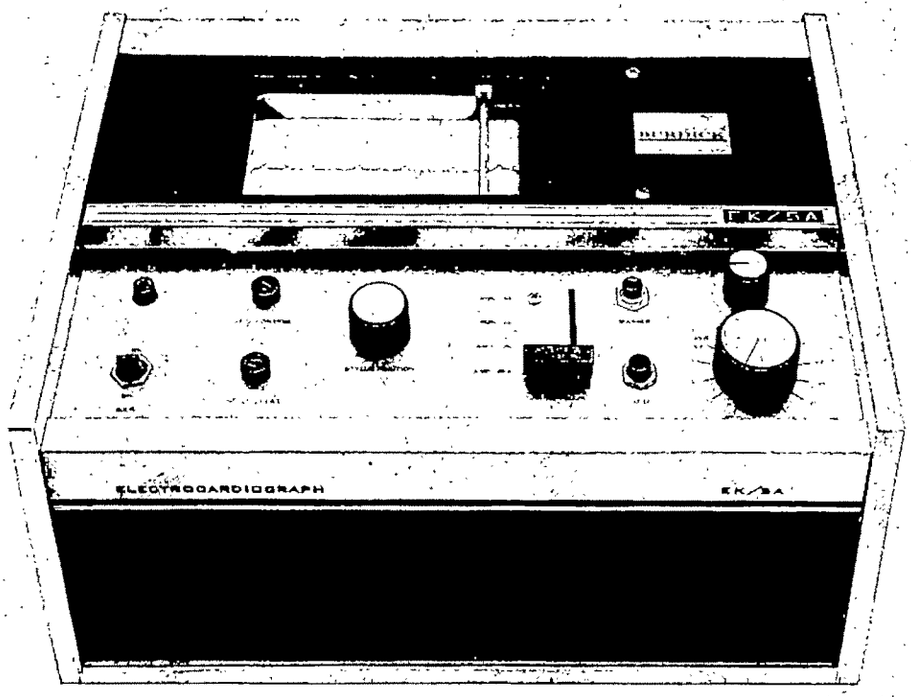
CASE REPORTS

454 Hypoplasia of the Left Ventricle: Rare Cause of Postoperative Mortality in Tetralogy of Fallot

THOMAS P. GRAHAM, Jr., SCOTT FAULKNER, HARVEY BENDER, Jr. and CHARLES M. WENDER

The overall mortality rate for repair of tetralogy of Fallot is approximately 5 percent. To re-

Continued on page A25



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duce this rate further, quantitative cineangiocardiography is important in selecting out the rare patient with severe left ventricular hypoplasia such as this 3 year old child with low cardiac output and a left ventricle less than 50 percent of normal size who died after attempted repair. As this case shows, severe left ventricular hypoplasia cannot be diagnosed without cineangiocardiographic quantitative volume measurements. Mild left ventricular hypoplasia with values for end-diastolic volume as low as 65 percent of normal is not a contraindication to primary repair. When the left ventricular end-diastolic volume is less than 55 percent of predicted normal, a shunt procedure may be preferable as an initial procedure with subsequent repair 1 or 2 years later after the left ventricle has a chance to enlarge.

458 **Chest Pain and Bilateral Atrioventricular Valve Prolapse With Normal Coronary Arteries in Isolated Corrected Transposition of the Great Vessels. Clinical, Angiographic and Metabolic Features**

MICHAEL J. COWLEY, H. CECIL COGHLAN, JOHN A. MANTLE and BENIGNO SOTO

Although the character, response to nitroglycerin, reproduction with atrial pacing and the abnormal clinical, metabolic and hemodynamic response to atrial pacing suggest "ischemic" myocardial dysfunction, the cause of severe disabling chest pain indistinguishable from unstable angina pectoris remains unknown in this 49 year old patient with bilateral atrioventricular valve prolapse, normal coronary arteries and corrected transposition of the great vessels. The patient had been well until he experienced chest pain during his early 40's. The mechanisms involved may be similar to those responsible for the still poorly understood syndrome of "angina with normal coronary arteriograms." This case adds to the widening spectrum of chest pain with normal coronary arteriograms and to the variety of abnormalities that may be seen with corrected transposition of the great vessels.

463 **Isolated Ventricular Discordance and Complete Atrioventricular Canal in Situs Inversus. Report of Successful Surgical Repair**

ERIC HAZAN, FRANÇOISE BAILLOT, CHRISTIAN REY and CLAUDE DUPUIS

Surgical repair of the heart using a Mustard procedure and correction of the endocardial cushion defect was successfully performed in a 9 year old girl with isolated ventricular discordance (a rare cardiac anomaly in which the right atrium opens into a morphologically left ventricle through a mitral-shaped orifice), a complete form of atrioventricular (A-V) canal and situs inversus. The postoperative development of complete A-V heart block required the insertion of a permanent pacemaker. The child's general condition and physical capacity progressively improved over the 2 years since operation.

EDITORIALS

467 **Mechanism of Early "Pump" Failure of the Ischemic Heart: Possible Role of Adenosine Triphosphate Depletion and Inorganic Phosphate Accumulation**

WOLFGANG KÜBLER and ARNOLD M. KATZ

472 **Early Valve Replacement for Preservation of Ventricular Function?**

SHAHBUDIN H. RAHIMTOOLA

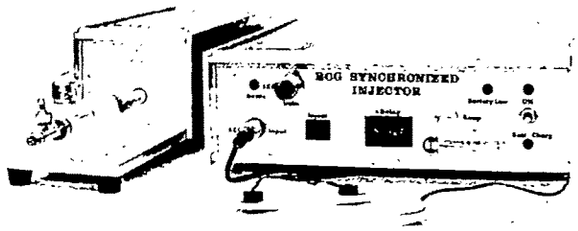
476 **Idiopathic Hypertrophic Subaortic Stenosis Afflicted: Idols of the Cave and the Marketplace**

BERNADINE H. BULKLEY

SPECIAL DEPARTMENTS

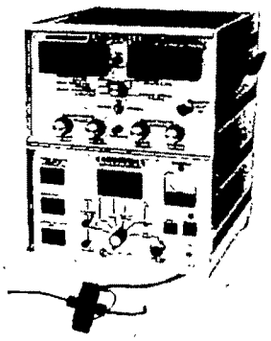
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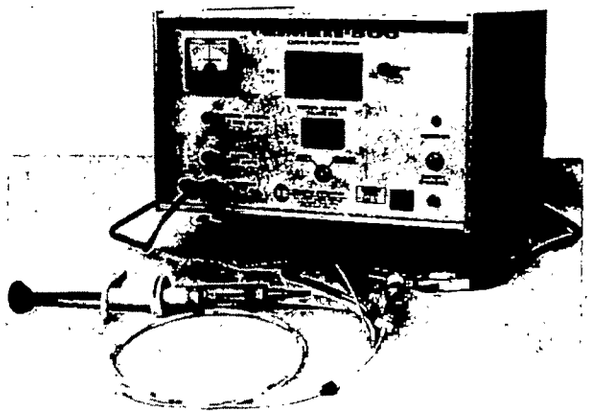


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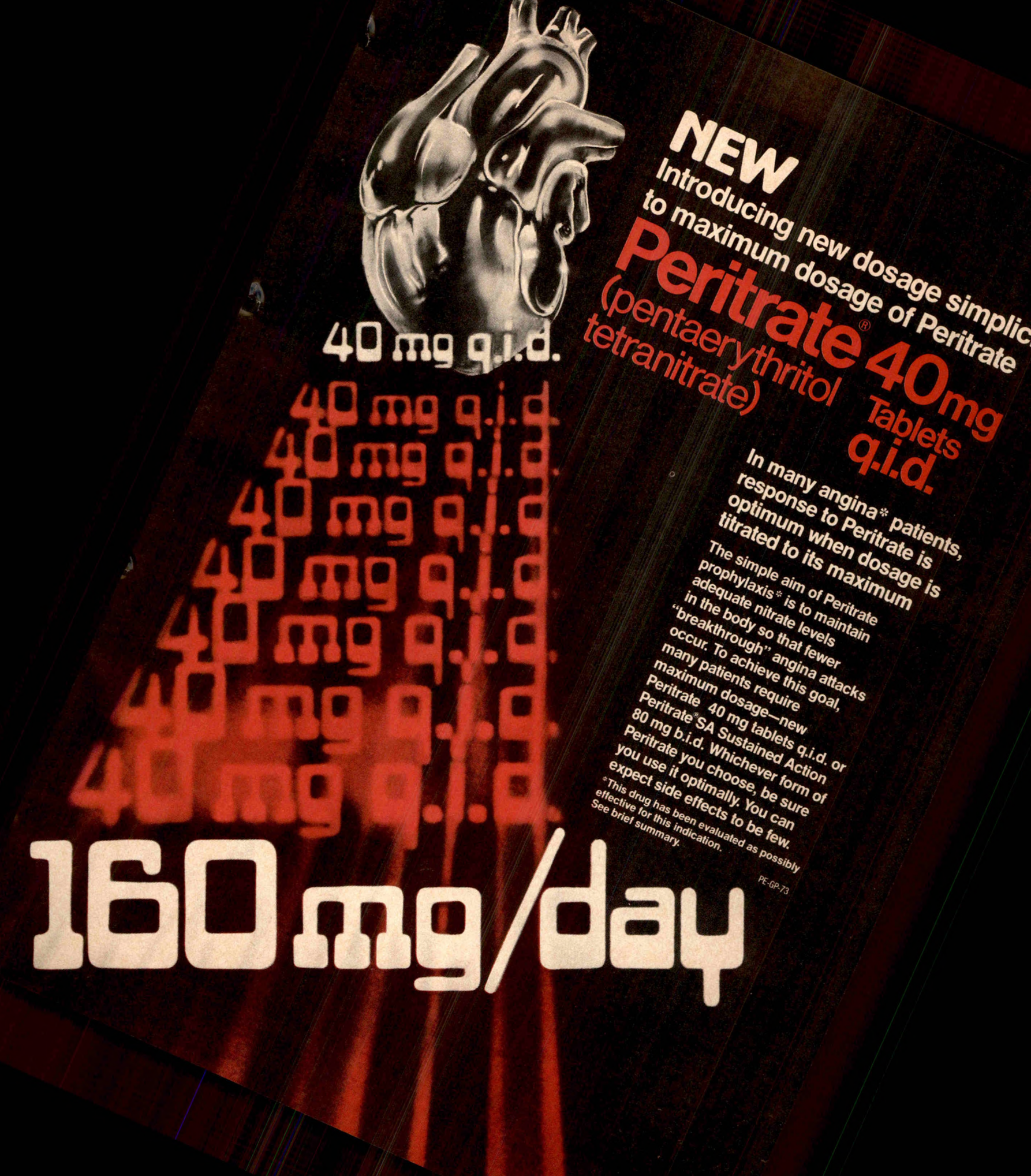
Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.
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Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artifically induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the post-arteriolar level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.
Full information is available on request.

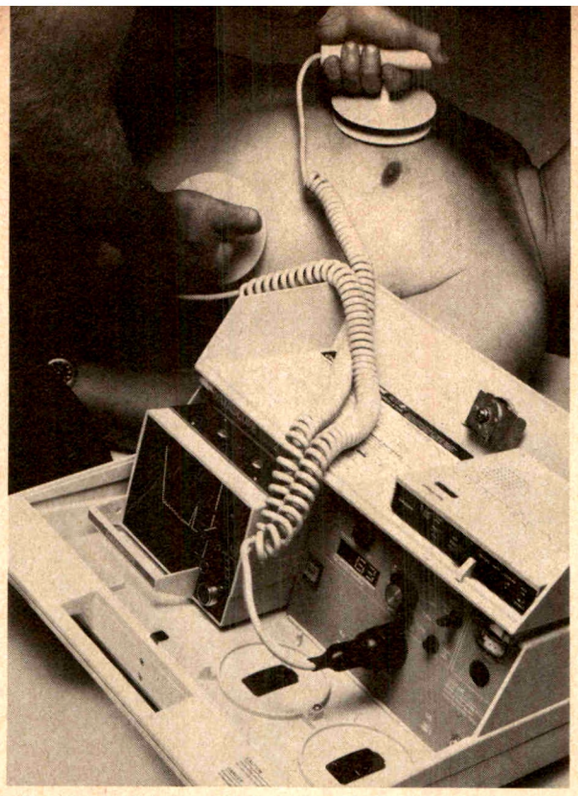
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For 7 out of 10 patients, your present defibrillator may be powerful enough.

But more important, fo 3 out of 10 it may not be.





Recent studies of de-
rillation have disclosed
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ccess rate for defibrillation
human adults is only about
% with defibrillators which
liver 300 watt-seconds
energy."* And "the prob-
ility of defibrillating a sub-
t who weighs over 220
unds is extremely low."*
ese studies have produced
e following finding: "virtu-
y all defibrillators now in
e have inadequate output
defibrillate many human
ults..."*

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veloped the Datascope M/D2J. A portable
fibrillator capable of delivering not 300, or the
dely available 320, but 460 watt-seconds of
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rtable defibrillator made today.

Which means,very simply, that you have
re capability when you need it.

But the Datascope M/D2J doesn't just de-
er more energy than other defibrillators. It tells
u more about what it's delivering.

It is the only defibrillator in the world that
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the subject during de-
rillation. (Energy
oduces current. But
rrent is what produces
defibrillation. Which is why current is the truly meaningful measure.) It also reads selected delivered energy. And delivered energy into a built-in test load. And instead of test lights, or ready lights, all readings are precisely shown on a bright digital display.

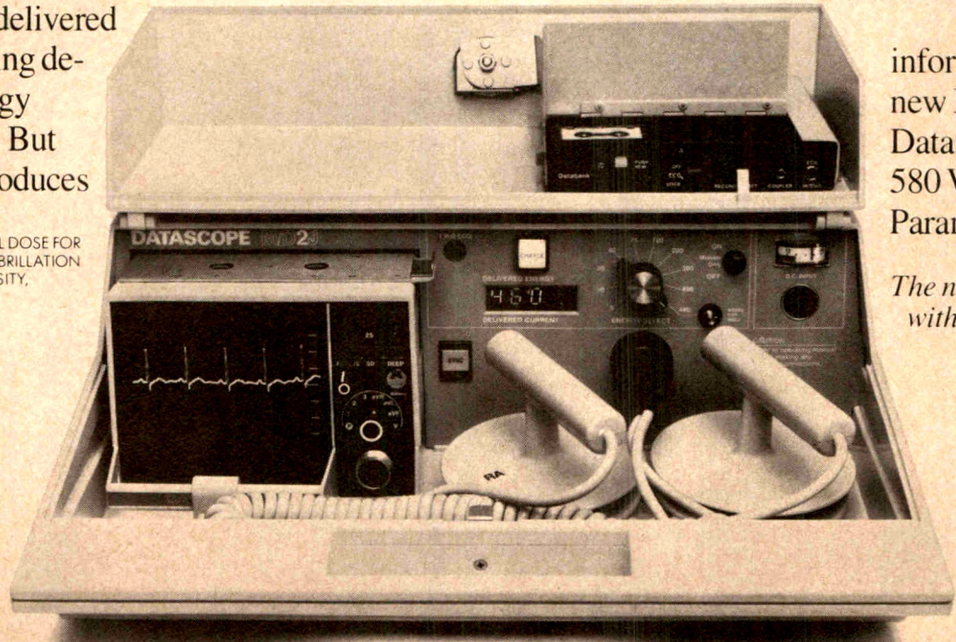
To this point, we've been discussing the M/D2J as if it were merely a defibrillator. Of course, it's a monitor/defibrillator. The defibrillator is an impressive part. But the other parts are equally impressive. The M/D2J offers the finest non-fade monitor of any monitor/defibrillator in emergency medicine.

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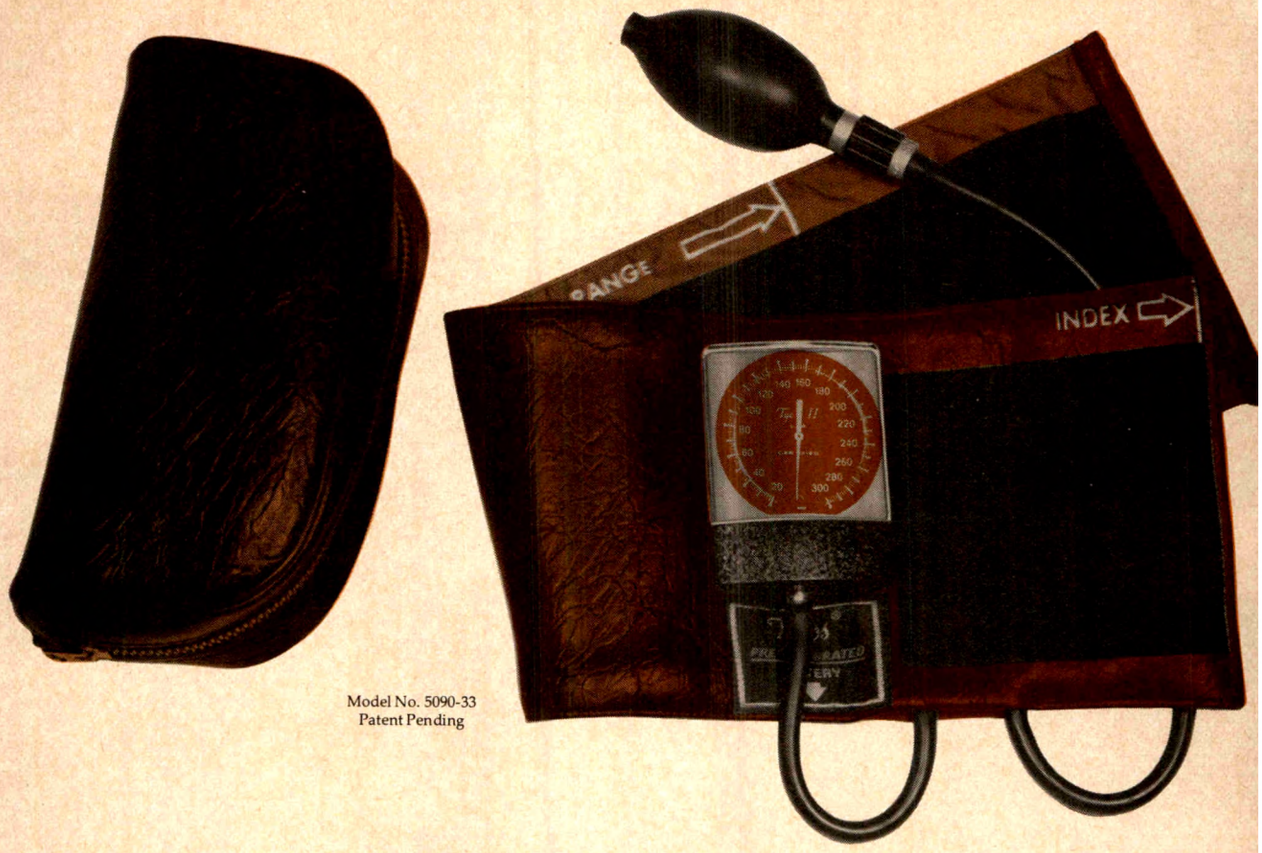
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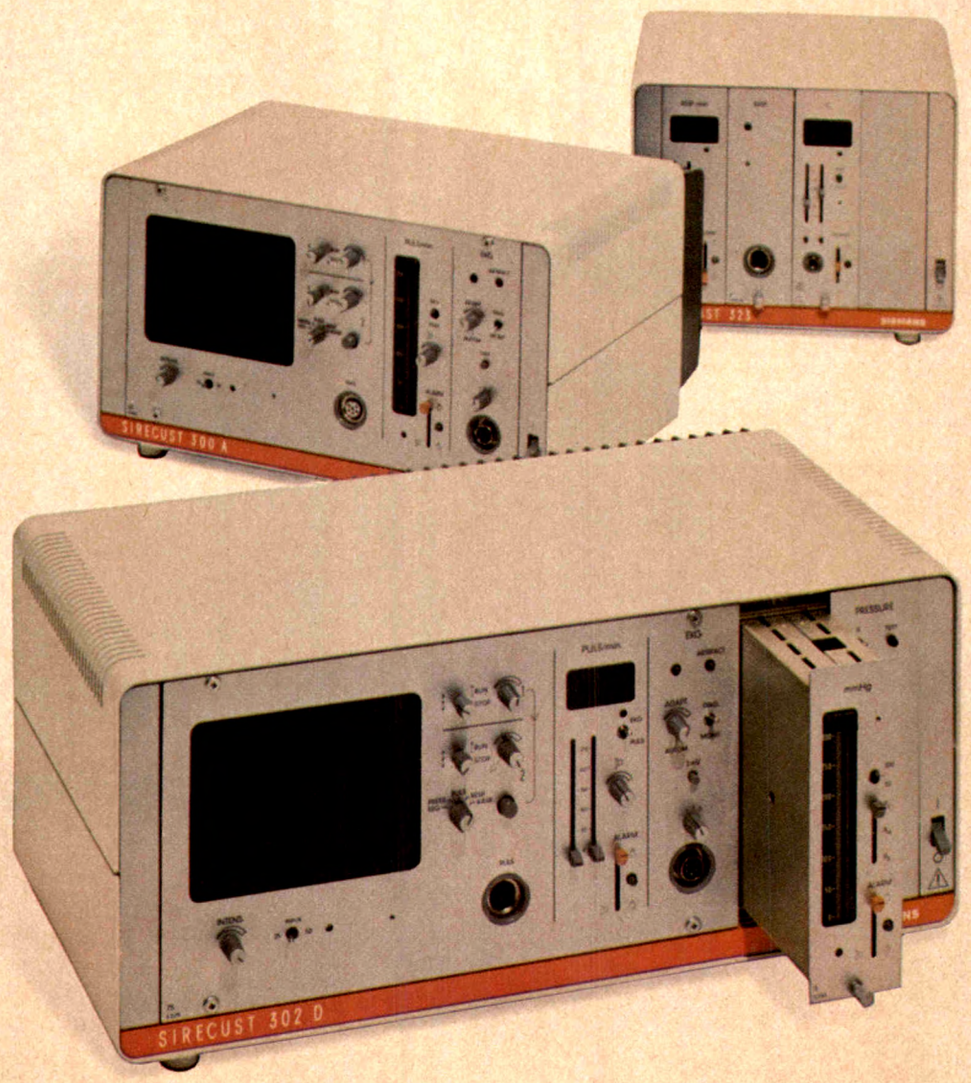
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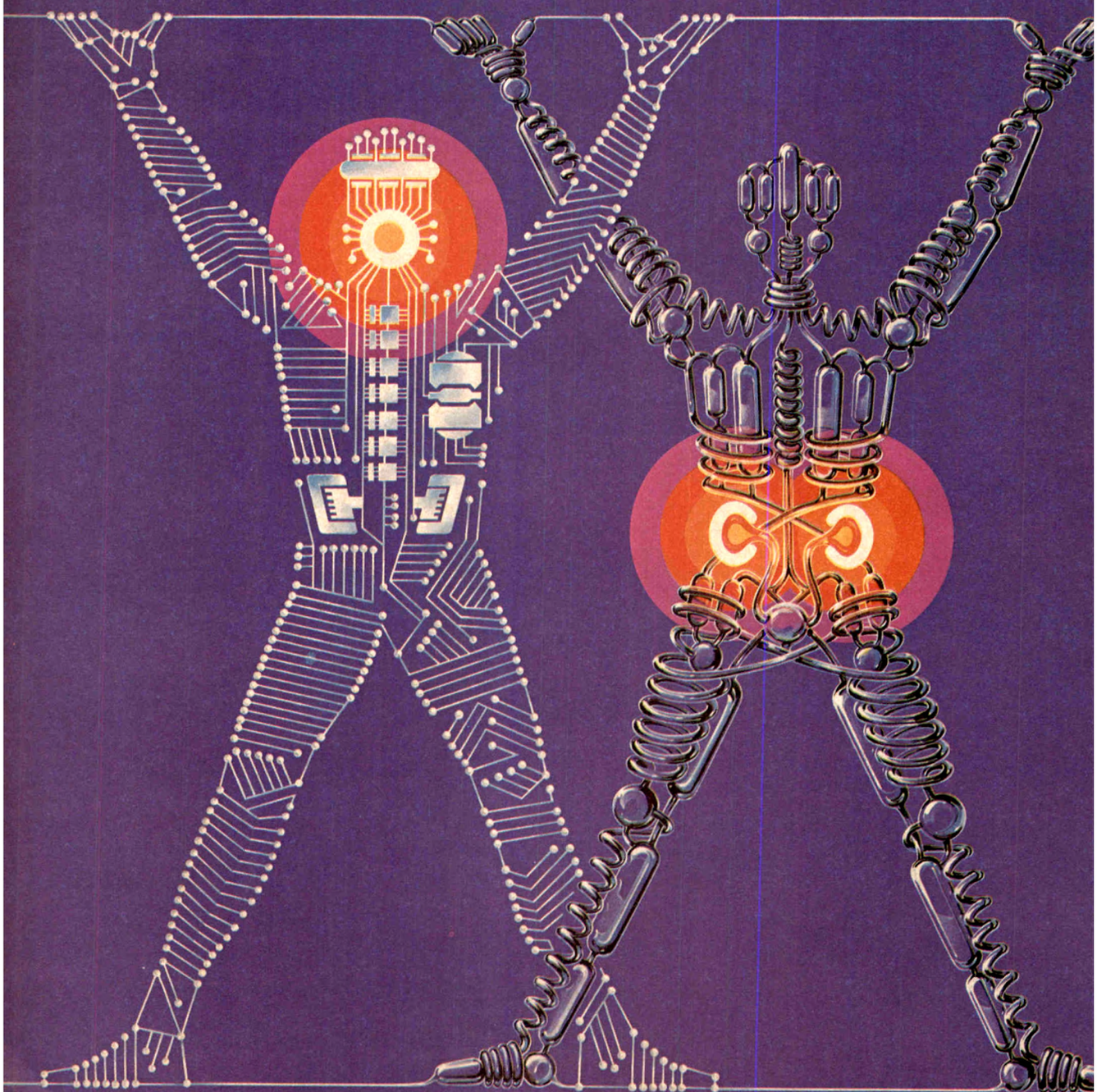
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Each tablet contains:
Catapres®, brand of clonidine hydrochloride,
0.1 or 0.2 mg and chlorthalidone, 15 mg

The only major new combination antihypertensive in a decade



Please see brief summary of the prescribing information including precautions, warnings, adverse reactions.

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Combipres® 1 and 2

Each tablet contains:
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Works better than either component in equivalent doses*

Works in mild to severe hypertension

Works conveniently for patients who need more than one drug*

Works for less than the cost of separate Rxs*

Works and works and works—convenience and economy promote long-term patient compliance

*Combipres is not indicated for initial therapy of hypertension. It is indicated for hypertensive patients who need more than one drug for adequate lowering of blood pressure and who have proved to be responsive to its components given separately in dosages equivalent to those in the combination.

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

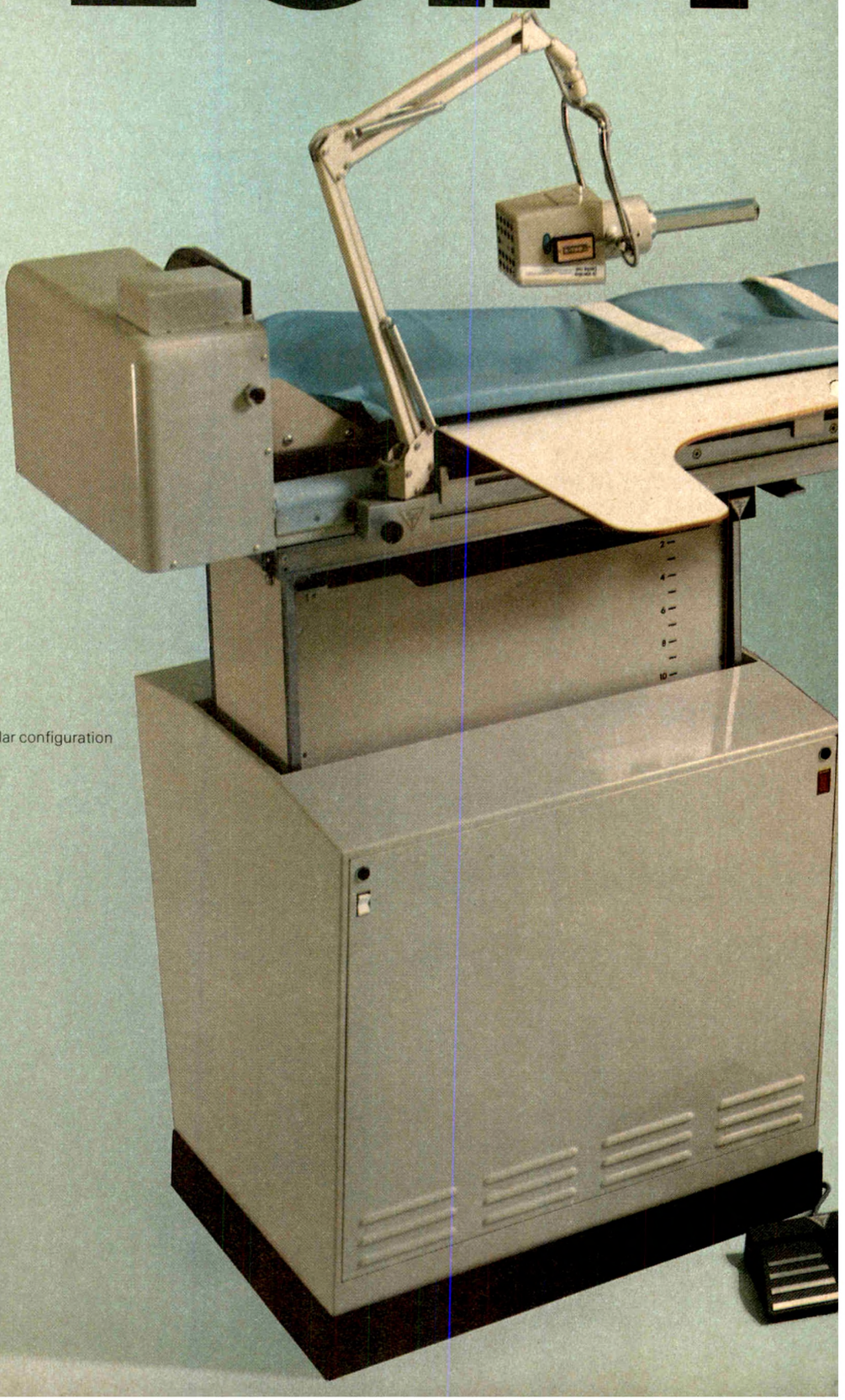
Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

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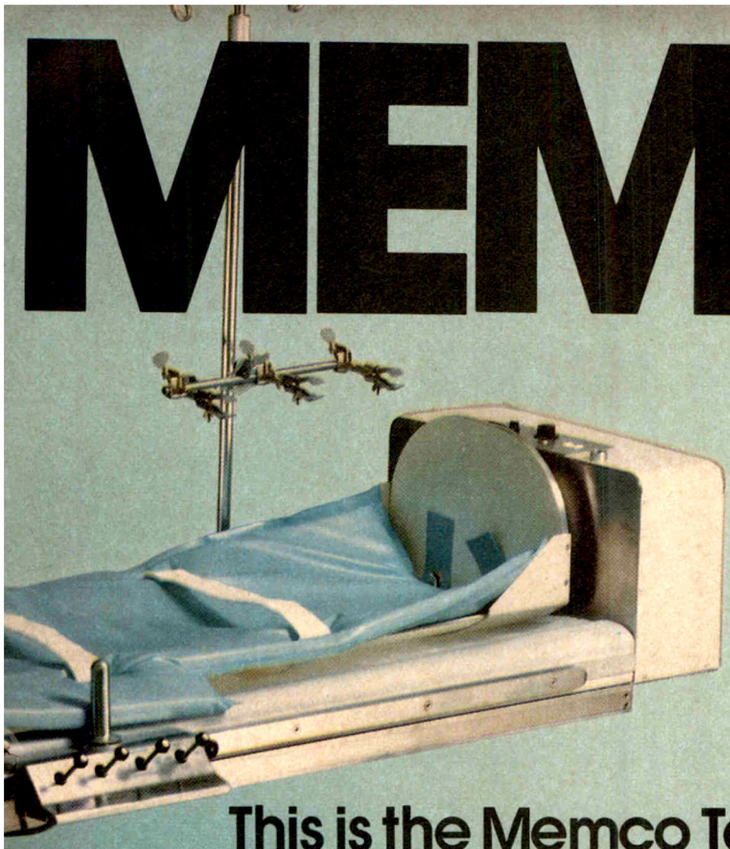
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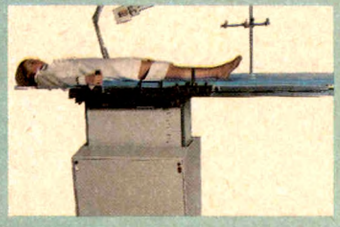


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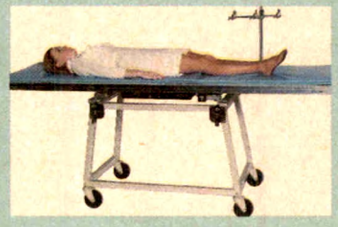
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There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate. The patient's age and medical condition, however, may dictate the particular pacing systems and implantation procedure used by the physician.

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The physician should be aware that all pulse generators will ultimately cease to function, and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, and elevated thresholds, and that proper operation may be affected by electrical interference from equipment using electrical energy, or medical complications.

SIDE EFFECTS

Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

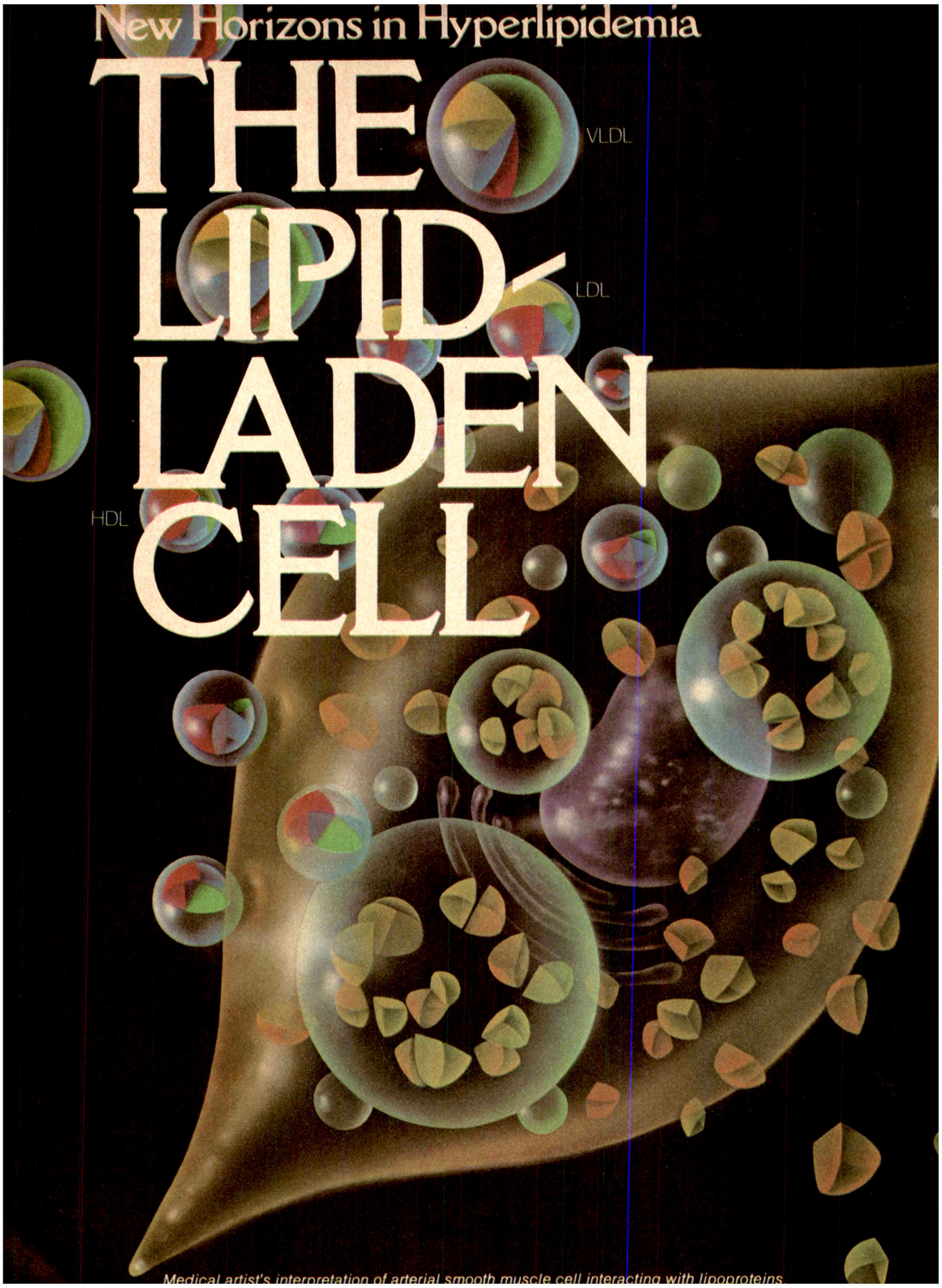
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New Horizons in Hyperlipidemia

THE LIPID-LADEN CELL



Medical artist's interpretation of arterial smooth muscle cell interacting with lipoproteins

Lipid overloading in the arterial smooth muscle cell: proposed biochemical mechanisms

The process by which a normal arterial smooth muscle cell is transformed into a lipid-laden "foam" cell is highly complex and, as yet, not completely understood. But from the findings of an ever-increasing number of animal and human studies,[1-28] investigators have begun to piece together a theoretical picture of what may occur—a picture that adds important new perspectives to an understanding of hyperlipidemia.

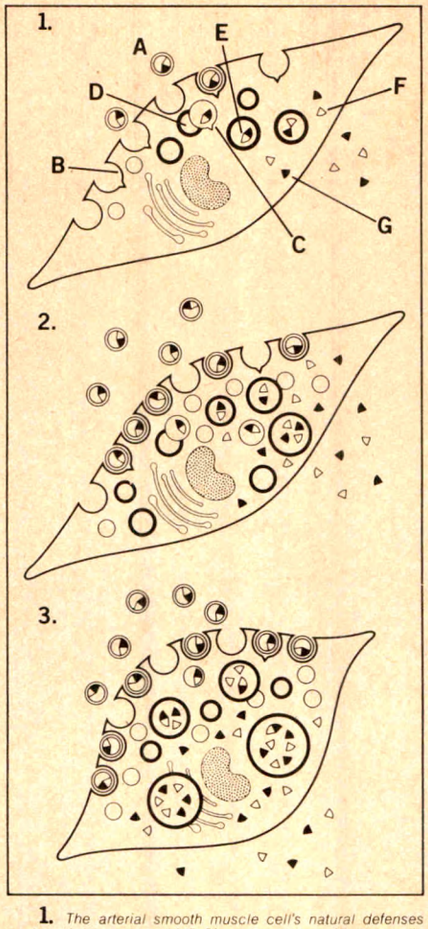
What emerges from this research is that induced and/or genetic abnormalities in the metabolism of arterial smooth muscle cells may be crucial to their evolution into a lipid-laden form.[6,9,11,19] Specifically, there appear to be alterations in the ability of these cells to bind, internalize and degrade triglyceride-rich very low density lipoproteins (VLDL) and cholesterol-rich low density lipoproteins (LDL).[1,2]

The endothelium, which normally acts as a selective barrier[20,25] to the entry of plasma constituents into the arterial wall, also appears to influence the behavior of arterial smooth muscle cells.[23,26] As a result of injury to the endothelium and/or increased concentrations of circulating lipoproteins, excessive quantities of lipids may breech the endothelial barrier, and accumulate in smooth muscle cells.[1,2,5,20,23] Eventually, the cells die and rupture, releasing their lipid content into the extracellular matrix of the arterial wall.

Human tissue cultures yield new insights into an insidious progression

Theories postulating the sequence of events that may produce lipid-laden cells were originally based on observations in a variety of animal species. Now, through the application of dramatic new biochemical techniques, many of these theories are finding support in studies of human cells. It is now possible to culture human arterial smooth muscle cells from explants of tissue obtained during vascular surgery,[1-3,10,18] human fibroblasts taken from the skin,[6,8,12,14] and human endothelial cells derived from umbilical veins.[15-17] Methods for studying the interaction of these cells with lipoproteins in culture have permitted the assessment of lipoprotein binding, uptake, and degradation.[1,2] (See diagrams at right). While this *in vitro* data requires *in vivo* confirmation, it can serve as a useful basis for investigation and discovery with regard to the relationship between plasma lipids and lipid accumulations in arterial walls.

esis[24] Disturbances in the normal metabolism of arterial smooth muscle cells can lead to marked changes in the lipid content of the arterial wall. The most notable change is an increase in cholesterol esters, but there are also increases in the concentration of other lipids, including triglycerides.[20] Following is a highly simplified outline of a working hypothesis to explain lipid overloading, as it relates primarily to LDL:[24]



1. *The arterial smooth muscle cell's natural defenses against lipid overload*[6-8,12] Given an artery with the endothelium intact, and a low level of circulating plasma lipoproteins, LDL uptake is predominantly of the high affinity, receptor-dependent type: LDL molecules (A) are bound to receptor sites (B) on the endothelial surface, internalized via pinocytotic vesicles (C), fused with lysosomes (D) which hydrolyze the cholesterol ester (E) component of the lipoprotein into its basic constituents, free cholesterol (F) and fatty acid (G). The free cholesterol triggers compensatory mechanisms which decrease cholesterol synthesis by the cell and also reduce the number of its LDL receptors, thereby helping to limit further entry of LDL. Under normal conditions, this acts to protect the arterial smooth muscle against lipid overload.

2. *The cell's response to an increased metabolic load.* Injury or disruption of the endothelium and/or a substantial increase in circulating plasma lipoproteins leads to entry of larger amounts of LDL and other lipid substances into the cells. At these higher plasma levels, lipids appear to be taken up predominantly via a low affinity, nonreceptor-mediated process.[7] Endocytosis is greatly stimulated and the number and size of the lysosomes increase in an effort to keep up with the increased load.[21]

3. *The cell's lipid-regulating mechanism overwhelmed.* If the state of increased metabolic activity needed to handle the extra lipid load persists, the "finely-tuned" regulatory mechanism may break down. With lipid passage into the cell virtually unchecked, massive intracellular accumulations of cholesterol and other lipids ensue. As a result, cellular function may be compromised, leading to cell death and deposition of lipids in the extracellular space.

High levels of circulating lipoproteins: a key factor in cellular overload

In human tissue cultures, arterial smooth muscle cells take up substantial quantities of VLDL and LDL and relatively small amounts of HDL.[1,2] This contrasts with the low uptake of VLDL and high uptake of HDL observed in smooth muscle cells of certain animal species (e.g., rats)[2] which have no propensity for lipid overloading in arterial cells.

Cellular concentrations of lipids also bear a relation to lipid concentrations in the serum. For example, both human and calf endothelial cells in tissue culture evidenced significantly higher levels of triglycerides and fatty acids after exposure to hypertriglyceridemic serum than did controls subjected to medium containing normal serum.[17]

These provocative studies have exciting implications for further investigation. *However, it must be remembered that there is to date no proof that lowering serum lipoprotein concentrations in humans will prevent or reverse the processes that produce lipid-laden cells.*

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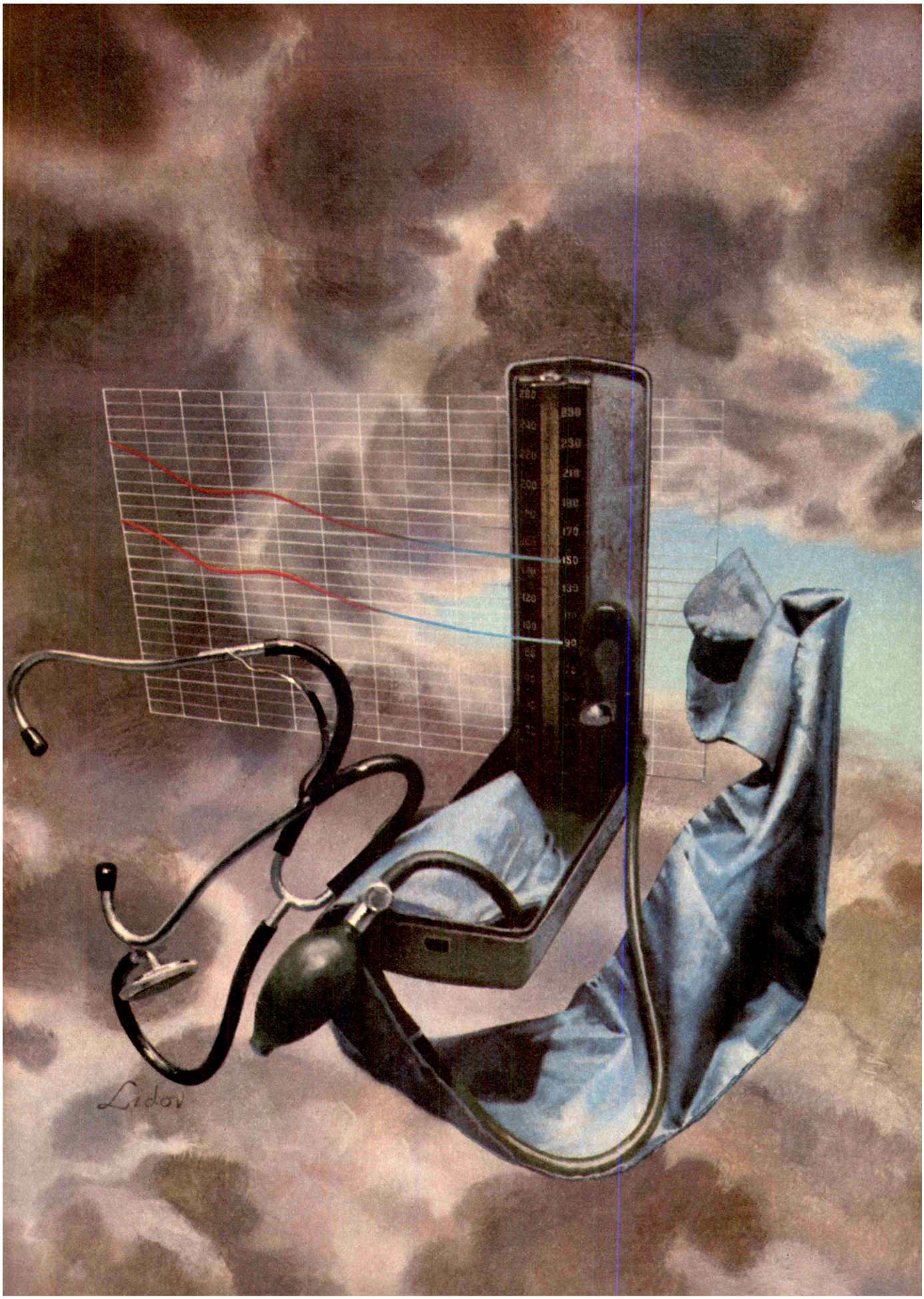
Note: Schematic illustrations of cells adapted from Wolinsky, H. Cardiovasc. Med. *1*:41 (Sept.) 1976.

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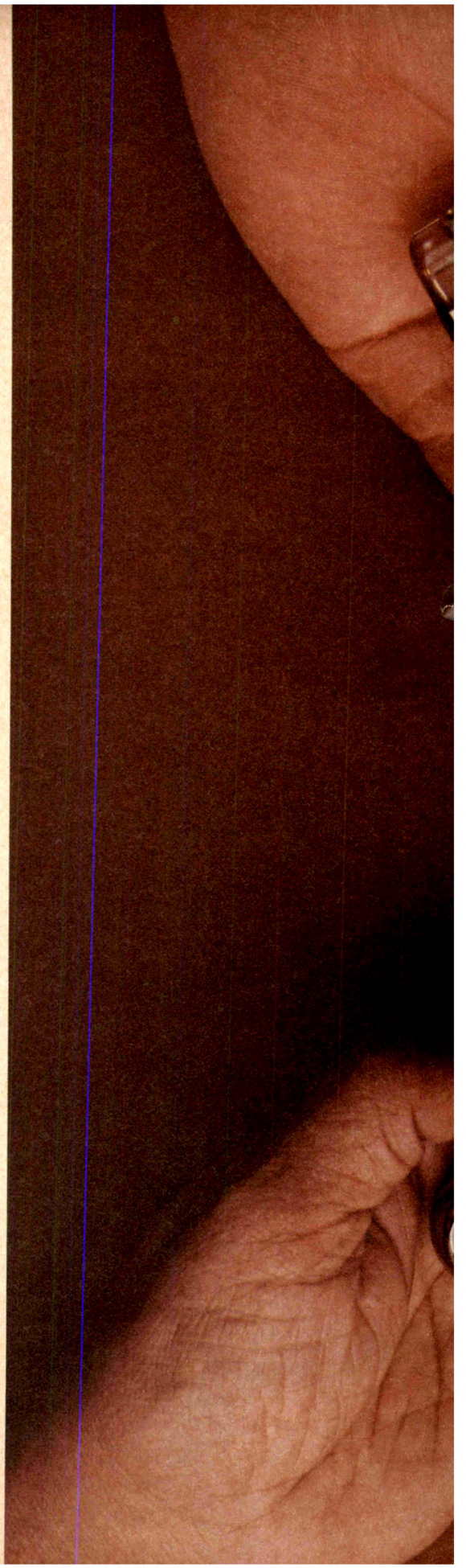
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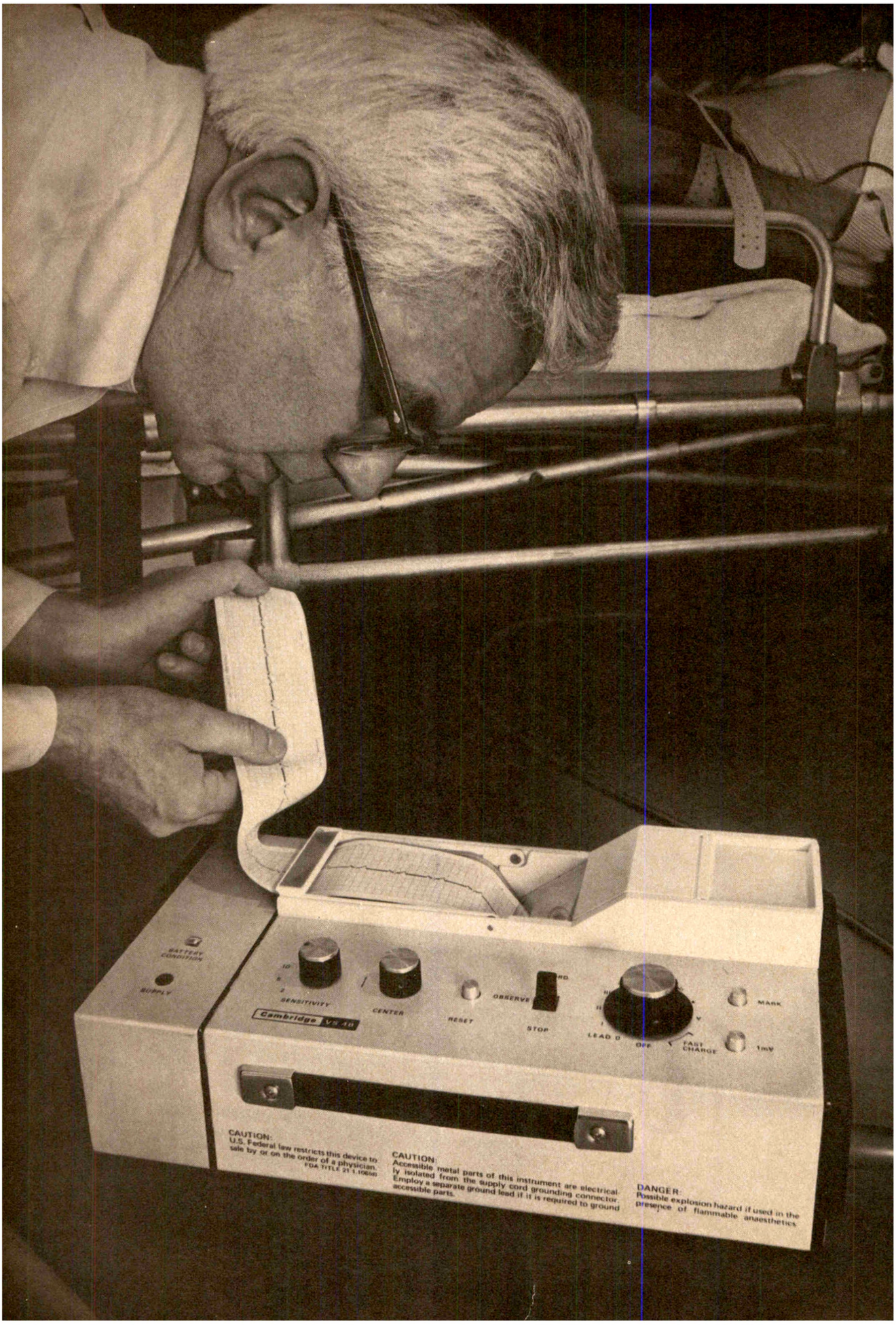
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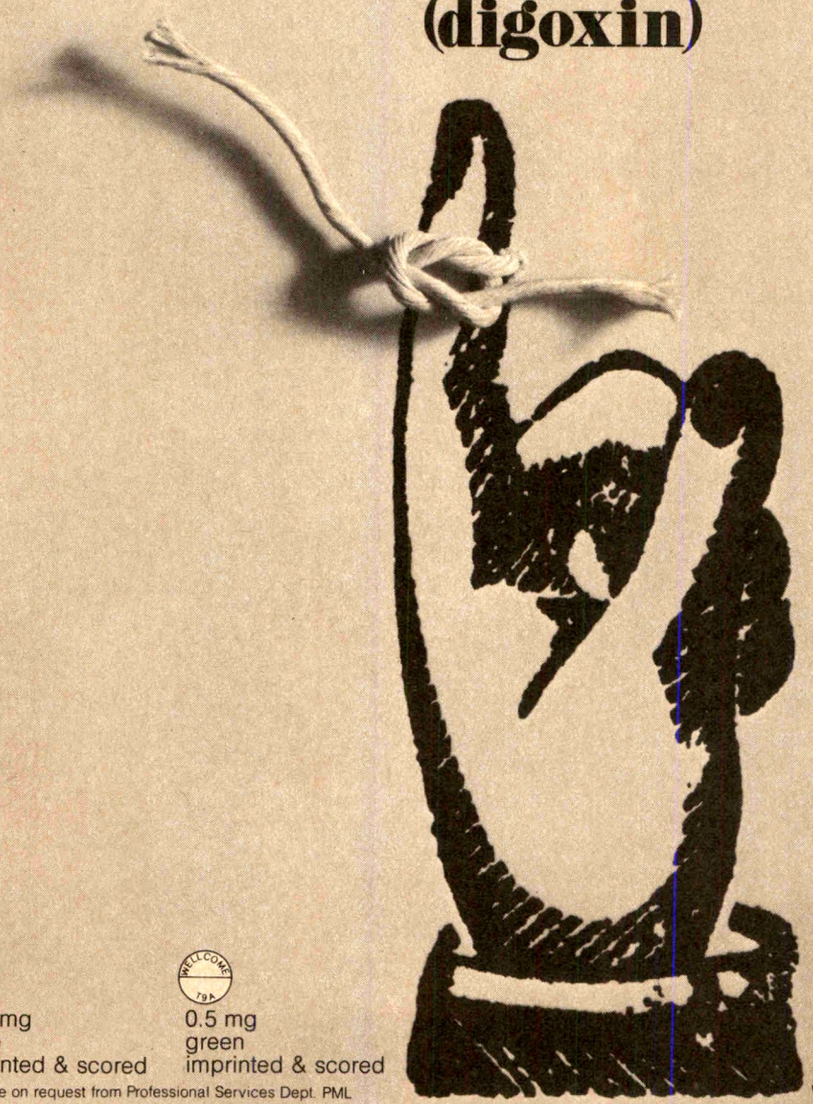
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CLINICAL STUDIES

Clinical Correlates of Left Ventricular Cavity Obliteration

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Left ventricular cavity obliteration is an angiographic phenomenon in which apical intracavitary space becomes totally occupied in systole by the contracting left ventricular muscle. To determine the clinical associations and physiologic significance of this finding we reviewed the clinical, echocardiographic, hemodynamic and angiographic data of 24 consecutive patients with cavity obliteration. The patients' ages ranged from 27 to 64 (mean 50) years. Their subjective complaints included chest pain (100 percent), dyspnea (96 percent), lightheadedness (33 percent) and palpitations (25 percent). Physical findings included an atrial gallop (92 percent) and a systolic murmur (67 percent). Left ventricular hypertrophy was evident in the electrocardiogram of 71 percent, but cardiomegaly was noted in the chest roentgenogram of only 29 percent. Other associated findings included hypertension (46 percent), aortic valve stenosis (21 percent), angiographic mitral valve prolapse (33 percent), mitral regurgitation (17 percent) and coronary artery disease (42 percent). An intraventricular pressure gradient was found in 9 of 15 patients (60 percent) studied with provocative maneuvers. Echocardiography, performed in 12 subjects, revealed asymmetric septal hypertrophy in 6 (50 percent) and symmetric hypertrophy in the remaining 6 (50 percent). An intraventricular pressure gradient was noted in four of the six patients with asymmetric and in five of the six with symmetric hypertrophy. The postextrasystolic beat phenomenon occurred both in patients with symmetric and in those with asymmetric hypertrophy, thus suggesting that cavity obliteration in itself may have important hemodynamic significance. Thus, cavity obliteration is a contraction abnormality that may be seen in a spectrum of ventricular hypertrophic disease states. Although it may be caused by idiopathic hypertrophic subaortic stenosis in some patients, the frequent association with hypertension, aortic stenosis and symmetric hypertrophy suggests a pathophysiologic relation to pressure overload in others.

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Left ventricular cavity obliteration may be defined as an angiographic phenomenon in which the apical intracavitary space becomes totally

occupied in systole by the contracting left ventricular muscle.[1] This phenomenon has been induced in experimental animals during inotropic stimulation[2,3] and hemorrhagic shock.[4] Its occurrence in the unstimulated heart during normal sinus rhythm has been the focus of much discussion and controversy, principally in regard to its role in so-called idiopathic hypertrophic subaortic stenosis.[1,5–7] Some investigators[1,8] have implicated cavity obliteration as a cause of the intraventricular pressure gradients,[1,8] whereas others[5,9] consider those gradients artifactual and due to entrapment of the catheter in cardiac trabeculae.

Despite widespread interest in and many published reports on idiopathic hypertrophic subaortic stenosis, several questions regarding cavity obliteration remain unanswered: (1) Is it relatively specific for idiopathic hypertrophic subaortic stenosis or does it occur in other clinical situations? (2) What are the clinical characteristics of patients who manifest it? (3) Is it merely an interesting angiographic observation or is it a physiologically significant phenomenon with important hemodynamic implications? This retrospective study was undertaken in an effort to investigate these questions.

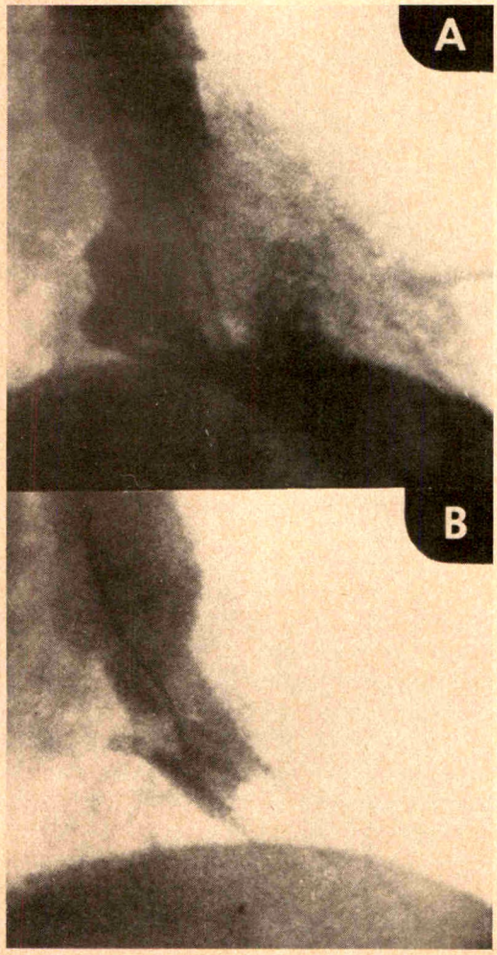


FIGURE 1. Left ventriculogram in the right anterior oblique projection demonstrating cavity obliteration. **A,** diastole; **B,** systole. Note that the apical intracavitary space becomes totally occupied in systole by the contracting left ventricular muscle.

Material and Methods

The left ventriculograms of 850 consecutive patients studied between January 1973 and June 1975 were reviewed. Cardiac catheterization was performed with patients in the postabsorptive state. No routine premedication was administered. Valium,® given orally, was used only in patients who were exceptionally anxious about the procedure. If the patient was receiving long-term treatment with other medications such as digitalis, propranolol or coronary vasodilators, these medications were not routinely discontinued before the study.

Left ventricular pressures were measured before angiography was performed. The standard protocol in our laboratory for detecting intraventricular and aortic valve pressure gradients consists of placing the catheter near the apex of the ventricle and obtaining pullback pressure recordings while withdrawing the catheter to the aorta. In some patients additional provocative maneuvers such as the Valsalva maneuver, amyl nitrite inhalation and isoproterenol infusion were performed while simultaneous left ventricular intracavitary and aortic or femoral arterial pressures were recorded in order to detect more thoroughly dynamic intraventricular pressure gradients. The left ventriculograms were routinely performed in the right anterior oblique projection with use of Renografin-76®, 32 to 45 cc over 3 to 4 seconds. No patient received sympathetic stimulation (isoproterenol infusion, for example) before or during left ventriculography. Coronary arteriography was performed in most patients, generally after left ventriculography.

Left ventricular cavity obliteration was considered present only when a complete loss of apical intracavitary space was noted during a regular sinus beat (Fig. 1). Patients demonstrating this phenomenon during postextrasystolic beats alone were not included in this study.

TABLE I

Clinical, Echocardiographic, Hemodynamic and Angiographic Data in 24 Patients With Left Ventricular Cavity Obliteration

	Patients	
	no.	%
Clinical data		
Chest pain	24	100
Exertional dizziness	8	33
Hypertension	11	46
Atrial gallop	22	92
Systolic murmur	16	67
LVH by ECG	17	71
Cardiomegaly on chest X-ray film	7	29
Echocardiographic data (no. = 12)		
Septal hypertrophy	12	100
Posterior wall hypertrophy	10	83
Asymmetric septal hypertrophy	6	50
Symmetric hypertrophy	6	50
Hemodynamic data		
Intraventricular pressure gradient (rest or provoked, no. = 15)	9	60*
Aortic transvalve gradient	5	21
Postextrasystolic beat phenomenon	9	38
Angiographic data		
Mitral regurgitation	4	17
Mitral valve prolapse	8	33
Critical coronary arterial lesions	10	42

* Represents 60 percent of 15 patients in whom gradients were sought with provocative maneuvers.
ECG = electrocardiogram; LVH = left ventricular hypertrophy.

The charts of the patients selected for study were reviewed with particular attention paid to subjective complaints and objective findings on physical examination. Electrocardiographic, roentgenographic and echocardiographic data were carefully analyzed. Most patients were available for follow-up studies in which these data were reconfirmed. The cardiac catheterization and angiographic findings were reviewed with particular attention given to end-diastolic pressures, pressure gradients and the presence or absence of a Brockenbrough or postextrasystolic beat phenomenon, defined as a decrease in the arterial pulse pressure in the sinus beat after an extrasystole.[10] Ejection fraction was calculated from the single plane right anterior oblique projection.[11]

Results

Clinical features: Left ventricular cavity obliteration satisfying our criteria was noted in 24 of the 850 consecutive angiograms obtained during the study period (prevalence rate 2.8 percent). All patients were male, a fact that reflects the population studied at our institution; their ages ranged from 27 to 64 years (mean 50 years). Pertinent clinical, echocardiographic, hemodynamic and angiographic data are shown in Table I.

Several subjective complaints dominated the clinical findings. All 24 patients complained of chest pain, but only 11 (46 percent) had typical angina pectoris. Dyspnea was reported by 23 patients (96 percent) and dizziness or lightheadedness by eight patients (33 percent); none described true syncope. Palpitations were described by six patients (25 percent).

Objective physical findings included the following: Hypertension (more than 160 mm Hg systolic or more than 90 mm Hg diastolic, or both, on two or more occasions) was documented in 11 patients (46 percent). An atrial gallop was heard in 22 subjects (92 percent) and a systolic murmur in 16 (67 percent). In only eight was the murmur attributed to valve disease (aortic stenosis in five and mitral regurgitation in three). In seven of the remaining eight patients without valve disease, the murmur was accentuated by standing, the Valsalva maneuver or amyl nitrite inhalation.

Electrocardiography disclosed left ventricular hypertrophy in 17 patients (71 percent), a pattern of old myocardial infarction in 3 (13 percent) and normal findings in 3. The chest roentgenogram showed cardiomegaly in only seven patients (29 percent).

Technically satisfactory echocardiograms were available in 12 of the 24 cases. Septal thickness ranged from 1.2 to 2.2 cm (mean ± standard error of the mean 1.68 ± 0.09). The left ventricular posterior wall thickness ranged from 1.0 to 1.6 cm (mean 1.29 ± 0.05). Septum to posterior wall ratios ranged from 0.93 to 1.80 (mean 1.31 ± 0.07). When a ratio of 1.3 or higher was used as an indicator of asymmetric septal hypertrophy,[12] 6 of these 12 patients qualified for this diagnosis. Systolic anterior motion of the anterior leaflet of the mitral valve was found in 3 of the 12 subjects (25 percent).

Catheterization findings: The left ventricular end-diastolic pressure at rest ranged from 4 to 33 mm Hg (mean 12.6 ± 1.5). Resting left ventricular end-diastolic pressure was elevated (more than 12 mm Hg) in 11 (46 percent) of the 24 patients. Ejection fraction ranged from 0.72 to 0.89 (mean 0.81 ± 0.01). A resting transvalve gradient indicating aortic valve stenosis was found in five subjects (21 percent) and ranged from 20 to 83 mm Hg. An intraventricular pressure gradient was found in 9 of 15 patients in whom such gradients were

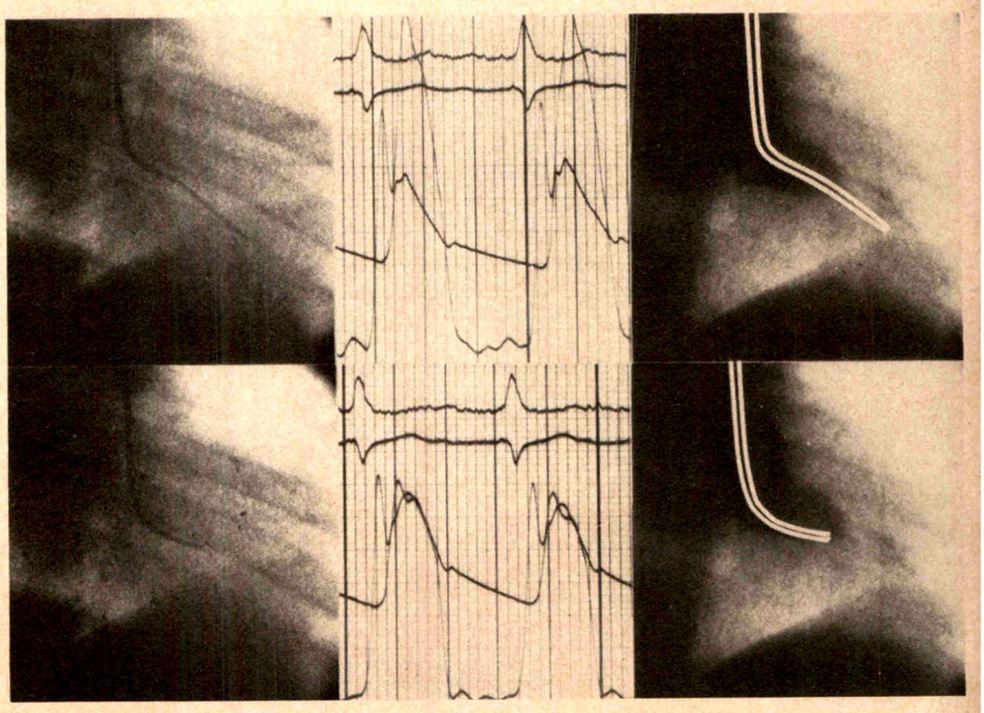


FIGURE 2. Catheter position in the left ventricle **(left panels)** during recording of high left ventricular pressure **(top panels)** and low pressure **(bottom panels).** The **middle panels** show the pressure recordings at these levels. On the right, the catheter position is superimposed over the left ventriculogram obtained during systole. The catheter position during recording of the high pressure is in the obliterated portion of the ventricle **(upper right).**

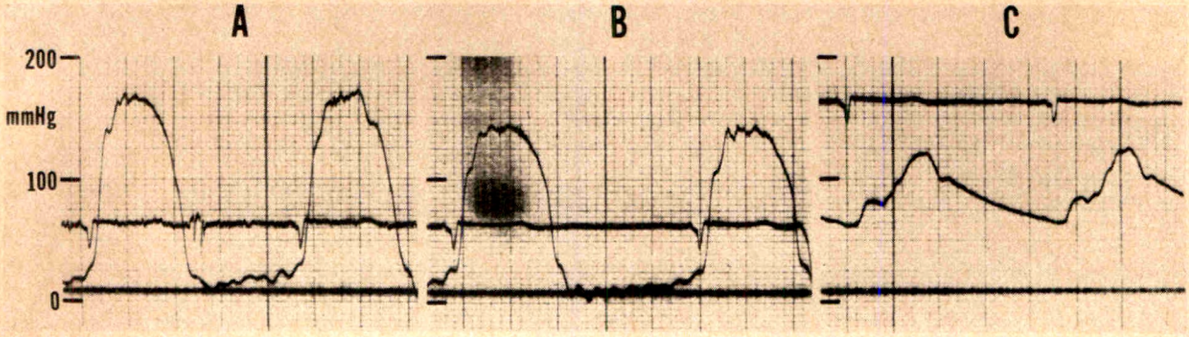


FIGURE 3. Left ventricular pressures obtained during pullback from apex to aorta in a patient with aortic valve stenosis and cavity obliteration. **A,** near the apex; **B,** outflow tract; **C,** aorta. Two pressure gradients are seen: intraventricular (**A** to **B**) and transvalve (**B** to **C**).

actively sought with provocative maneuvers. In four of these nine, the gradient was present at rest and ranged from 10 to 27 mm Hg. In the remaining five, a gradient could be provoked with the Valsalva maneuver, amyl nitrite inhalation or isoproterenol infusion. Many patients tended to manifest the pressure decrease on pullback from the area of obliterated cavity to the outflow tract, rather than in the subvalve area (Fig. 2). Two patients had both intraventricular and transvalve pressure gradients (Fig. 3). A postextrasystolic beat phenomenon (Fig. 4 and 5) was found in nine patients (38 percent); in four of these nine the postextrasystolic beat phenomenon was demonstrable during isoproterenol infusion.

Pertinent angiographic data included the following: Mitral regurgitation was noted in only four subjects and was mild in three of these. An angiographic pattern of mitral valve prolapse was recognized in eight patients (33 percent), but only one of these eight had mitral regurgitation. In most instances, the degree of prolapse was mild. Significant coronary artery disease was found in 10 (42 percent) of the patients with cavity obliteration. Myocardial bridges, manifested angiographically as systolic narrowing of a coronary artery,[13,14] were recognized in 3 of the 24 patients (13 percent).

Correlation of echocardiographic and angiographic findings: To place some of the preceding data in more appropriate perspective, we analyzed a subgroup of 12 patients with cavity obliteration who had complete echocardiographic and hemodynamic data. Six of these 12 could be categorized as having asymmetric septal hypertrophy and 6 had symmetric hypertrophy. Of the six with asymmetric septal hypertrophy, four had an intraventricular pressure gradient and three of these four had the postextrasystolic beat phenomenon (Fig. 4). Two patients had asymmetric septal hypertrophy but no demonstrable intraventricular gradient. Of the six patients with symmetric hypertrophy, five had an intraventricular pressure gradient (found at rest in two and with provocation in three). Symmetric hypertrophy in these five patients was attributable to aortic valve stenosis in two, to hypertension in two and to no specific cause in one. Three of these five patients also demonstrated a postextrasystolic beat phenomenon (Fig. 5). One patient with symmetric hypertrophy had no intraventricular pressure gradient but manifested a postextrasystolic beat phenomenon.

Discussion

This study attempted to examine the prevalence and clinical associations of left ventricular cavity obliteration. This phenomenon was first brought to clinical attention by Criley et al.[1] as a feature of some patients with so-called idiopathic hypertrophic subaortic stenosis and as a possible cause of the intraventricular pressure gradient in these patients. Further studies have indicated that this angiographic finding is not specific for idiopathic hypertrophic subaortic stenosis but can occur in normal hearts during states of enhanced sympathetic stimulation or volume depletion, or both, such as those induced by inotropic stimulation[2,3] or experimental hemorrhagic shock.[4] We studied only patients who manifested cavity obliteration in regular sinus beats during left ventriculography and who were not receiving sympathomimetic infusions and did not have shock. Our findings suggest that several pathologic mechanisms might be operative in producing a pattern of left ventricular cavity obliteration.

Pathologic Mechanisms

Left ventricular hypertrophy: This may be an important factor in cavity obliteration. All 12 patients in this study who had echocardiograms demonstrated septal hypertrophy, and 83 percent had concomitant hypertrophy of the posterior left ventricular wall. Electrocardiographic evidence of left ventricular hypertrophy was found in 71 percent of subjects. Despite the high prevalence rate of echocardiographic and electrocardiographic evidence of ventricular hypertrophy, only 29 percent of the patients had cardiomegaly on chest roentgenogram, thus suggesting that cavity obliteration may occur in hypertrophied hearts when there is no concomitant dilatation.

The basic disease processes causing left ventricular hypertrophy and cavity obliteration appear to be more heterogeneous than previously recognized. In addition to idiopathic hypertrophic subaortic stenosis or hypertrophic cardiomyopathy, conditions of pressure overload such as hypertension and aortic valve stenosis appear to be associated with this angiographic phenomenon.

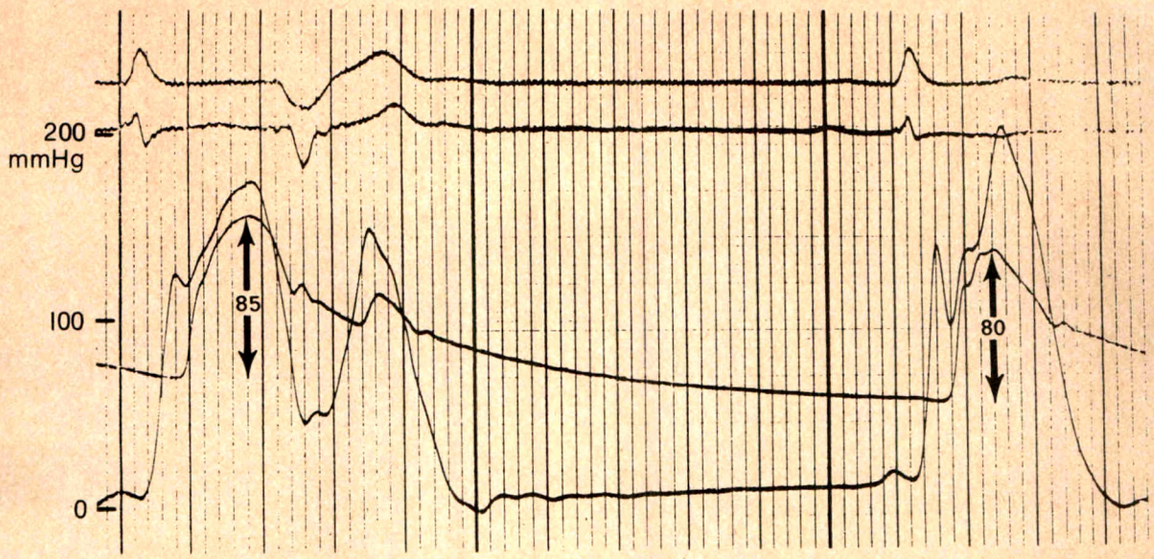


FIGURE 4. A Brockenbrough (postextrasystolic beat) phenomenon in a patient presenting the clinical findings of idiopathic hypertrophic subaortic stenosis with asymmetric septal hypertrophy and cavity obliteration. Note the decreased aortic pulse pressure (80 versus 85 mm Hg) in the beat after the extrasystole.

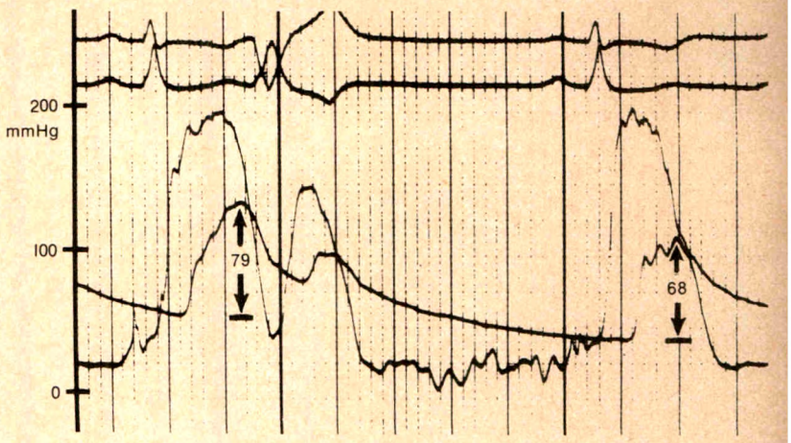


FIGURE 5. A postextrasystolic beat in a patient with aortic stenosis, symmetric hypertrophy and cavity obliteration. Note the decrease in the aortic pulse pressure in the postextrasystolic beat (68 versus 79 mm Hg) in the absence of an increase in left ventricular systolic pressure.

Asymmetric versus symmetric hypertrophy: When a ratio of 1.3 or higher was used as an echocardiographic indicator of asymmetric septal hypertrophy,[12] 6 of the 12 subjects studied with ultrasound qualified for this diagnosis. An intraventricular pressure gradient was demonstrable in four of these. The combination of asymmetric septal hypertrophy and an intraventricular pressure gradient may represent, using commonly accepted definitions, patients with so-called obstructive idiopathic hypertrophic subaortic stenosis, hypertrophic obstructive cardiomyopathy or obstructive asymmetric septal hypertrophy.[15–18] A more appropriate label may be hypertrophic cardiomyopathy with gradient because the finding of an intraventricular gradient in a patient with cavity obliteration may not represent true anatomic outflow tract obstruction.[1,8] The two patients with asymmetric septal hypertrophy without a demonstrable intraventricular pressure gradient may represent instances of hypertrophic nonobstructive cardiomyopathy. Again, in the absence of histopathologic specimens from the left ventricle, a cardiomyopathic process cannot be ascertained.

The remaining six patients were found to have symmetric septal hypertrophy, and five of these had an intraventricular pressure gradient. Two of the five had aortic valve stenosis and two had severe systemic hypertension, conditions that provide reasonable explanations for the symmetric hypertrophy. It is not clear why an intraventricular pressure gradient was found in these patients, but the data tend to support the concept of Criley et al.[8] that a pressure gradient can result from the isometric contraction within the obliterated portion of the ventricle relative to the nonobliterated intracavitary region and need not be a manifestation of obstruction at the outflow tract.

Postextrasystolic beat phenomenon: Four of the six patients with symmetric ventricular hypertrophy manifested a postextrasystolic beat phenomenon, in-

cluding three of the five with an intraventricular pressure gradient and one without a gradient. This phenomenon has been said to be specific for idiopathic hypertrophic subaortic stenosis,[10] and its occurrence in this group of patients is intriguing. Several possibilities must be considered:

1. The echocardiographic reading was in error and these patients actually have asymmetric septal hypertrophy and should be considered to have idiopathic hypertrophic subaortic stenosis. This explanation is not likely because only technically good echocardiographic studies were utilized and four of these five patients had diseases (aortic stenosis in two and hypertension in two) that are known to result in symmetric hypertrophy.

2. The postextrasystolic beat phenomenon in these patients may represent a catheter artifact. This explanation, too, is unlikely because we defined the phenomenon as a decrease in the aortic or arterial pulse pressure in the postextrasystolic beat. The catheter in the aorta or femoral artery is not prone to artifactual phenomena such as catheter entrapment.

3. These patients may have idiopathic hypertrophic subaortic stenosis with symmetric hypertrophy. The absence of asymmetric septal hypertrophy may not exclude this diagnosis.[19,20]

4. The postextrasystolic beat phenomenon may not be specific for idiopathic hypertrophic subaortic stenosis. In the beat after a premature ventricular contraction, the normal ventricle ejects a significantly larger stroke volume as a result of increased diastolic filling (during the compensatory pause) and augmented ventricular contraction.[10] Both of these mechanisms may be impaired in the cavity obliterating ventricle. First, diastolic filling may be limited by the reduced compliance of the hypertrophied ventricle.[21,22] Second, a ventricle whose cavity obliterates ejects maximally or nearly maximally with normally conducted sinus beats. Inotropic stimulation, such as that occurring in the postextrasystolic beat, may not significantly augment ejection. Thus, cavity obliteration in itself may offer a hemodynamic explanation for the postextrasystolic beat phenomenon in some patients, and the occurrence of this phenomenon should not be considered infallibly indicative of dynamic outflow tract obstruction.

The remaining patient in this study had symmetric hypertrophy and no intraventricular pressure gradient. He also demonstrated a postextrasystolic beat phenomenon, thus supporting the hypothesis that cavity obliteration in itself, without obstructive phenomena, might have important hemodynamic significance. Because this patient did not have hypertension, aortic stenosis or any reason to account for the hypertrophy he might be considered to have cardiomyopathy with symmetric hypertrophy.

Cavity obliteration versus true outflow tract obstruction: An intraventricular pressure gradient was found in 9 of 15 patients in this series in whom such gradients were actively sought with provocative maneuvers. In most instances, the approximate site of the gradient corresponded to the area of cavity obliteration (Fig. 2). As such, the finding of a pressure gradient need not represent obstruction at the level of the outflow tract.[1,8] Left atrial catheterization, either by the transseptal technique or the retrograde approach, may provide a more reliable means of ascertaining a true outflow site of obstruction.[8,23] Nevertheless, these techniques are not routinely performed in most catheterization laboratories and it is possible that many patients found to have an intraventricular pressure gradient may not have anatomic outflow tract obstruction if the pattern of cavity obliteration is present. Of interest in this regard, idiopathic hypertrophic subaortic stenosis has been said to coexist with fixed aortic valve stenosis,[24–26] coarctation of the aorta,[26] fixed congenital subvalve aortic stenosis[26,27] and systemic hypertension.[28] In view of our observations that pressure overload may be an important cause of cavity obliteration and cavity obliteration in itself may produce hemodynamics virtually indistinguishable from those of idiopathic hypertrophic subaortic stenosis, one wonders if some or many of the patients said to have coexisting pressure overload and idiopathic hypertrophic subaortic stenosis may merely have cavity obliteration rather than true outflow tract obstruction. In fact, the left ventriculograms of patients reported to have pressure overload disease and presumed coexistent idiopathic hypertrophic subaortic stenosis have shown cavity obliteration.[24,25]

Catheter entrapment: It is often difficult to exclude catheter entrapment as a cause of an artifactual elevation of intracavitary pressure. Analysis of the pressure curve, demonstration of systolic spurting of blood through the catheter and the use of multihole catheters have minimized the likelihood of this possibility in our study. Furthermore, the finding of a postextrasystolic beat phenomenon in the aortic or femoral arterial pressures could not be explained by left ventricular catheter artifact.

Clinical Aspects

Despite the different pathologic processes that may be found, patients with left ventricular cavity obliteration may present a surprisingly similar spectrum of findings. Subjectively, there was a very large prevalence of chest pain and dyspnea and objectively a large prevalence of atrial gallops and systolic murmurs.

The origin of the systolic murmur in some patients could be attributed to underlying valve disease, such as aortic stenosis and mitral regurgitation. Nevertheless, eight patients had neither of these valve lesions and still had a murmur that was audible at the lower left sternal border and often accentuated with the Valsalva maneuver, standing or amyl nitrite, or all three. Although this murmur is suggestive of idiopathic hypertrophic subaortic stenosis, it should be noted that five of the eight had no intraventricular pressure gradient. It is possible that unusually rapid early systolic ejection of blood from the ventricle[29] contributes to the genesis of such murmurs.

Coronary artery disease was found in 10 of our patients, most of whom had symptomatic angina pectoris. Seven of the 10 had double or triple vessel disease.

Therefore, severe coronary artery disease is not incompatible with this contraction phenomenon. Myocardial bridges were found in 13 percent of our subjects, a prevalence rate considerably higher than that in a general catheterization population.[14]

In summary, cavity obliteration is a contraction abnormality that may be seen in a spectrum of ventricular hypertrophic disease states. Whereas hypertrophic cardiomyopathy or idiopathic hypertrophic subaortic stenosis may be the cause in some patients, the frequent association with hypertension, aortic stenosis and symmetric hypertrophy suggests the possibility of a pathophysiologic relation to pressure overload in others. The clinical presentation of patients with angiographic evidence of cavity obliteration often includes similar subjective and objective findings despite the heterogeneity of the pathologic process. A cavity obliterating ventricle frequently exhibits hemodynamic phenomena, such as an intraventricular pressure gradient and postextrasystolic beat phenomenon, that may be physiologic consequences of cavity obliteration as such and need not necessarily imply outflow tract obstruction.

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Septal Perforator Compression (Narrowing) in Idiopathic Hypertrophic Subaortic Stenosis

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Thirteen patients with idiopathic hypertrophic subaortic stenosis were compared with two groups of subjects: 10 patients with chest pain, normal coronary arteries and a normal left ventricle, and 10 patients with left ventricular hypertrophy. Five of the latter had aortic stenosis and five had idiopathic left ventricular hypertrophy. Coronary arteriography revealed that the septal branches of the left anterior descending artery closed or narrowed during systole in patients with idiopathic hypertrophic subaortic stenosis and did not do so in the other patient groups. This narrowing is possibly related to an abnormal position of the septal arteries within the septum in idiopathic hypertrophic subaortic stenosis. Systolic compression of the septal perforator arteries is not a pathognomonic sign of idiopathic hypertrophic subaortic stenosis.

Several workers[1–5] have described the clinical, hemodynamic, angiographic and pathologic manifestations of idiopathic hypertrophic subaortic stenosis. Other investigators[6,7] have studied these patients with coronary arteriography and described the association of idiopathic hypertrophic subaortic stenosis with coronary artery disease.

The availability of echocardiography has provided the clinician with an accurate and sensitive means of confirming the suspected diagnosis of idiopathic hypertrophic subaortic stenosis.[8–10] As a consequence, hemodynamic and angiographic studies are not currently performed on a routine basis in all patients with suspected idiopathic hypertrophic subaortic stenosis.

We have studied 13 patients with idiopathic hypertrophic subaortic stenosis who had high quality coronary arteriograms that revealed narrowing of the septal perforator branches of the left anterior descending coronary artery during systole. To our knowledge, this phenomenon has not previously been described and represents an additional angiographic sign in this syndrome.

Material and Methods

The files of the cardiac laboratories of The Mount Sinai Hospital, New York and Peter Bent Brigham Hospital, Boston were reviewed in consecutive fashion for the 24 months between January 1974 and February 1976, and all cases with hemodynamic and angiographic features of idiopathic hypertrophic subaortic stenosis were analyzed. Thirteen patients were selected who had diagnostic high quality selective coronary arteriograms; eight others were rejected because of nonselective or unsatisfactory coronary arteriograms. Two control groups were also studied: one a group of 10 consecutive patients with a chest pain syndrome, normal coronary arteries and a normal left ventricle and the other a group of 10 consecutive patients with angiographic evidence of left ventricular hypertrophy due to significant aortic stenosis or other cause.

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All patients with idiopathic hypertrophic subaortic stenosis underwent right and left heart catheterization in the postabsorptive state under light sedation with orally administered diazepam. The left side of the heart was entered in retrograde fashion by means of a brachial arterial arteriotomy or femoral arterial percutaneous puncture. The left ventricular outflow tract gradient was measured with simultaneous aortic and left ventricular pressure recording or pullback from the left atrium to the aorta.[11] Left ventriculography was performed in the right and left anterior oblique projections. Selective coronary arteriography was performed with the Sones[12] or Judkins[13] technique.

The branches of the left anterior descending coronary artery that perfuse the septum are perforating arteries. They branch perpendicularly and extend for a variable distance into the septum. Their number and size are variable. Their diameter normally does not vary through the cardiac cycle (Fig. 1) as visualized with cineangiography.

"Septal perforator narrowing" is defined as a reduction in diameter of the septal arteries during systole. This reduction leads to nonvisualization of these vessels during systole on cineangiography (Fig. 2). Each angiogram was reviewed by three of us. Septal narrowing was graded 1+ to 3+, 1+ indicating systolic disappearance of the lower third, 2+ disappearance of the lower two thirds and 3+ disappearance of the entire septal artery.

Bridging or narrowing of other coronary vessels was also looked for.

Results

Idiopathic hypertrophic subaortic stenosis: Table I summarizes the clinical findings of the 13 patients in this group. Eight patients were men and five were women. Their ages ranged from 47 to 66 years (average 53 years). All patients had symptoms related to the basic condition. Eight had angina pectoris, seven had dyspnea

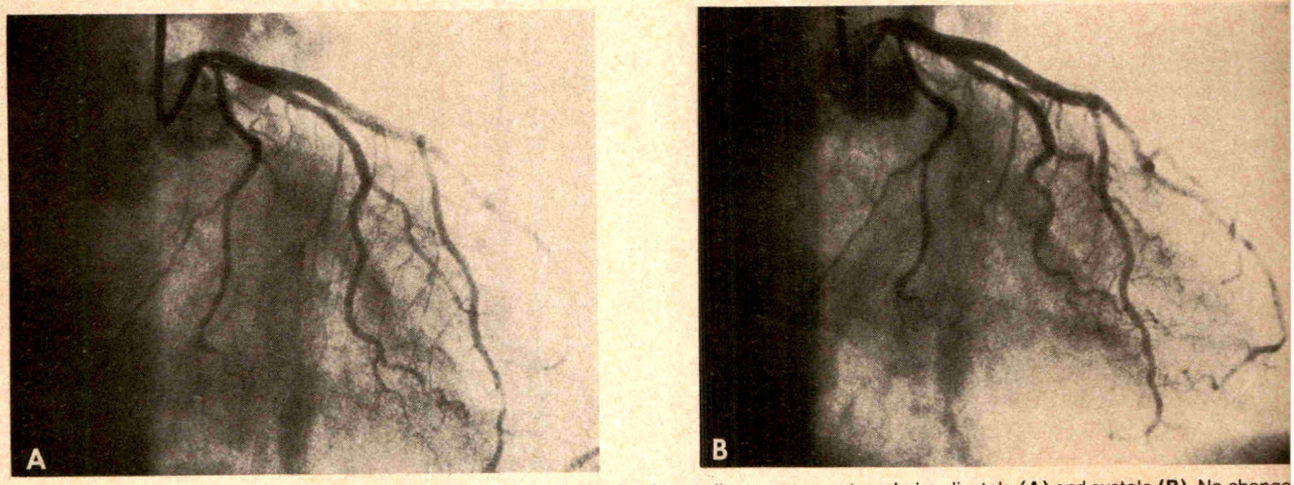


FIGURE 1. Control patient. Septal perforator branches of the left anterior descending coronary artery during diastole **(A)** and systole **(B).** No change in luminal diameter is observed in control groups.

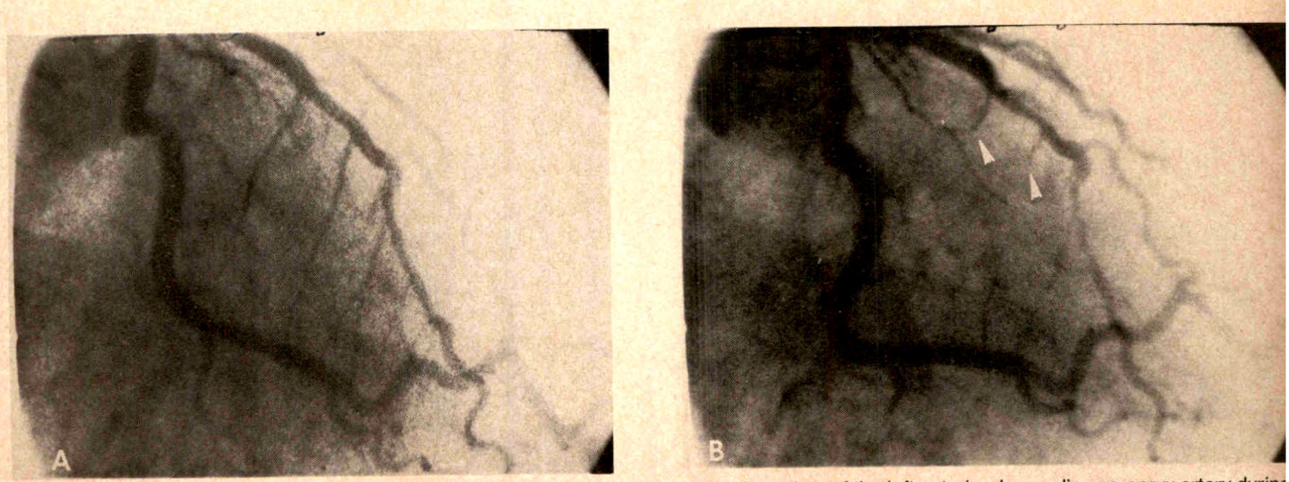


FIGURE 2. Patient with idiopathic hypertrophic subaortic stenosis. Septal perforator branches of the left anterior descending coronary artery during diastole **(A).** During systole **(B),** there is narrowing and almost complete obliteration **(arrows).**

TABLE I

Clinical Characteristics in 13 Patients With Idiopathic Hypertrophic Subaortic Stenosis

Case no.	Age (yr) & Sex	Angina Pectoris	Dyspnea on Effort or CHF	Dizziness or Syncope	Electro-cardiogram	Chest X-ray Film	Echo-cardio-gram
1	66M	No	Yes	Yes	LAE, LVH	CE 2+	IHSS
2	52F	Yes	No	No	LVH	CE 1+	*
3	51M	Yes	Yes	No	LVH	Normal	*
4	49F	Yes	No	No	Inferior MI	CE 1+	*
5	51M	No	No	No	LVH + strain	Normal	IHSS
6	60M	Yes	No	No	LVH + strain	CE 1+	IHSS
7	49M	No	No	No	LVH + strain	CE 1+	IHSS
8	53F	Yes	Yes	No	LVH, septal Q waves	Normal	IHSS
9	52M	Yes	Yes	No	LVH + strain	CE 2+	IHSS
10	56M	Yes	Yes	No	LVH + strain	CE 1+	*
11	47F	Yes	No	No	Q waves in leads II, III, aVF	Normal	*
12	50F	No	Yes	No	LVH + strain	Normal	*
13	58M	No	Yes	Yes	LVH	Normal	*

* Echocardiogram not obtained.
CE = cardiac enlargement; CHF = congestive heart failure; IHSS = idiopathic hypertrophic subaortic stenosis; LAE = left atrial enlargement; LVH = left ventricular hypertrophy; MI = myocardial infarction.

or other manifestations of congestive heart failure and two had dizzy spells or syncope. The electrocardiogram was abnormal in all patients, revealing left ventricular hypertrophy in five, left ventricular hypertrophy with strain in six and abnormal Q waves alone in two. The chest roentgenogram showed a normal heart size in six patients and cardiac enlargement in seven. Echocardiograms, obtained in six patients, were diagnostic of idiopathic hypertrophic subaortic stenosis in all.

The hemodynamic and angiographic findings of these patients are presented in Table II. Seven patients had an intraventricular pressure gradient at rest (13 to 90 mm Hg, average 62). With provocation (Valsalva maneuver, isoproterenol infusion, postextrasystolic potentiation), an intraventricular gradient (30 to 180 mm Hg, average 109) could be induced in all patients. One patient had an associated significant gradient at rest across the outflow tract of the right ventricle.

One patient had severe two vessel coronary artery disease. Two patients had mild to moderate narrowing of the left anterior descending artery in its middle third during systole (milking effect).[14] No narrowing or bridging of other coronary arteries was observed.

Septal perforator narrowing was found in all 13 patients with idiopathic hypertrophic subaortic stenosis (Fig. 2). It was marked (3+) in five patients, moderate (2+) in six and mild (1+) in two. Grade 3+ septal narrowing was always found in association with a pressure gradient at rest and severe outflow obstruction during provocation. Patients with no gradient at rest had 1+ or 2+ septal arterial narrowing. Mitral regurgitation of mild to moderate degree was present in nine patients.

TABLE II

Hemodynamic and Angiographic Findings in 13 Patients With Idiopathic Hypertrophic Subaortic Stenosis

Case no.	Pressures (mm Hg) LV (Rest)	Aorta (Rest)	IV Gradient Rest	IV Gradient Maneuver	PA	RV	CO	Coronary Arteriography	Septal Perforator Narrowing During Systole	MR
1	200/24	130/60	76–90	130–160	70/30	70/10	3.09	30% RCA	3+	no
2	178/36	118/64	60	124	48/18	50/2	3.8	normal	3+	no
3	188/6	135/70	50	60	20/6	20/2	4.6	30% mid LAD	3+	1+
4	170/18	170/95	0	96-180	18/4	23/0	4.8	Normal	2+	1–2+
5	130/12	130/70	0	30	20/12	40/20	5.3	Normal	1+	no
6	140/10	140/80	0	100	32/13	32/9	4.2	100% LAD, 100% LCx_p	1+	no
7	180/16	180/78	0	65	30/10	30/6	5.2	Mild narrowing mid LAD	2+	2+
8	180/4	115/65	65	80	32/15	32/6	4.3	Normal	3+	1+
9	160/25	160/80	0	120	36/18	36/14	2.7	Mod. narrowing mid LAD	2+	1+
10	179/9	121/80	58	140	26/14	26/7	5.1	Normal	3+	2+
11	188/25	152/77	13–37	125	30/15	35/12	6.5	Normal	2+	1+
12	208/30	111/68	97	161	40/21	42/8	7.9	Normal	2+	2+
13	134/13	135/76	0	133	23/5	23/2	4.8	Normal	2+	1+

CO = cardiac output (liters/min); IV = intraventricular; LAD = left anterior descending coronary artery; LCx_p = posterolateral left circumflex artery; LV = left ventricle; Mod. = moderate; MR = mitral regurgitation; PA = pulmonary artery; RCA = right coronary artery; RV = right ventricle.

Normal control group: The first control group had 10 patients with a chest pain syndrome, normal coronary arteries, no outflow tract gradient and normal left ventricular function. None of these patients had septal perforator narrowing (Fig. 1). The echocardiogram was normal in 7 of the 10 and showed mitral valve prolapse in 2; it was not obtained in 1 patient.

Control group with left ventricular hypertrophy: A second control group had five consecutive patients with aortic stenosis and five consecutive patients with left ventricular hypertrophy of other cause. Among the patients with aortic stenosis, the outflow tract gradient ranged from 85 to 185 mm Hg (average 107). Among the patients with idiopathic left ventricular hypertrophy, no outflow tract gradient was found (at rest or with provocation). Angiographic left ventricular hypertrophy was significant in all 10 patients. None had obstructive coronary artery disease or septal perforator narrowing. Bridging or narrowing of the left anterior descending or other coronary arteries was not observed in any of these 10 patients.

Discussion

The first publications[15,16] on coronary arteriography in patients with idiopathic hypertrophic subaortic stenosis demonstrated a normal coronary arterial tree although prominent Q waves in the electrocardiogram suggested myocardial infarction. Atherosclerotic obstruction of the coronary arteries was later described in association with idiopathic hypertrophic subaortic stenosis.[6,7,17,18] Coronary arteriography is now recommended routinely for evaluating adult patients with the diagnosis of idiopathic hypertrophic subaortic stenosis who undergo cardiac catheterization.

Our study demonstrates the presence of systolic narrowing (compression) of the septal perforator branches of the left anterior descending coronary artery during systole in patients with idiopathic hypertrophic subaortic stenosis. To our knowledge, this finding has not previously been reported. Although varying in degree (1+ to 3+) this was a consistent finding in this group of patients with idiopathic hypertrophic subaortic stenosis. The most severe degree of septal perforator narrowing (3+) was found in patients with an intraventricular gradient at rest or severe outflow tract obstruction on provocation with specific interventions such as the Valsalva maneuver or isoproterenol infusion.

Septal perforator compression was not seen in the control groups of patients, that is, those with normal coronary arteries and normal left ventricle, those with severe aortic stenosis and those with idiopathic left ventricular hypertrophy. We recently observed one patient with hyperdynamic cardiomyopathy without outflow obstruction at rest or on provocation, who presented the phenomenon of septal perforator narrowing during systole. No elevation in right-sided pressures or other abnormalities were seen in this patient. The echocardiogram revealed a hyperdynamic left ventricle, normal thickness of the posterior left ventricular wall and septum and decreased end-systolic volume. In view of this case, septal perforator narrowing during systole, although unique, does not appear to be specific for idiopathic hypertrophic subaortic stenosis.

Mechanism of septal perforator narrowing in idiopathic hypertrophic subaortic stenosis: The mechanism is not clear. Under normal circumstances, the septal perforator branches of the left anterior descending artery course close to the endocardium on the right side of the septum until their terminal arborization.[19] In this way, these vessels are not subjected to left ventricular pressures (except for the terminal ramifications that leave the parent vessel at a right angle) and have the flow pattern of epicardial vessels. Systolic narrowing of a coronary vessel occurs when it courses through the left ventricular myocardium (wall tension is greater than aortic pressure during systole[20]) as demonstrated on coronary arteriography by the "bridging" or "milking" effect[14] of the left anterior descending artery. In consequence, the septal perforator narrowing observed in patients with idiopathic hypertrophic subaortic stenosis suggests that these vessels are subjected to intramyocardial tension during systole. Several theoretical possibilities would explain this phenomenon:

1. It is possible that the septal perforator branches course anomalously through the left ventricular side of the septum instead of lying in their normal position close to the right ventricular endocardium. This could be a coronary arterial malformation. Such a phenomenon could result in selective ischemia of the septum and might be related in some way to the pathogenesis of asymmetric septal hypertrophy and fibrosis because hypoxia is a well known stimulus for hypertrophy.[21,22] A similar phenomenon is seen in the hypertrophic fibrotic left ventricle of cases with anomalous origin of the left coronary artery from the pulmonary artery.[23] No pathologic studies are available to confirm this hypothesis.

2. The characteristic histologic findings in the septum of idiopathic hypertrophic subaortic stenosis are the presence of disorderly arranged muscle fibers, variable degrees of interstitial fibrosis and a bizarre type of cell hypertrophy.[24,25] It is possible that this disorganized hypertrophy engulfs the septal perforator branches as a *secondary* phenomenon, subjecting these vessels to increased pressure during systole. Again, the subendocardial fibrosis of the septum may be due to the secondary new segmental ischemia.

In summary, we have described the association of idiopathic hypertrophic subaortic stenosis with systolic narrowing of the septal perforator branches of the left anterior descending coronary artery as a consistent phenomenon. We have no definitive explanation for the physiopathologic mechanism involved but have analyzed some possibilities. This phenomenon, although unique, does not appear to be exclusive for idiopathic hypertrophic subaortic stenosis and can occur in any situation under similar physiologic conditions.

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Phasic Aortocoronary Bypass Graft Blood Velocity During Ventricular Arrhythmias in Man

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With use of the Doppler ultrasonic flowmeter catheter, phasic aortocoronary bypass graft blood velocity was measured in 16 conscious subjects during ventricular arrhythmias. Ventricular extrasystoles reduced peak systolic and diastolic graft blood velocities by 20 to 80 percent, generally in relation to their respective coupling intervals. When extrasystoles appeared in closely coupled salvos diastolic bypass blood velocity virtually ceased. Nineteen episodes of ventricular tachycardia produced an average 50 percent decrease in peak graft blood velocity (control mean ± 1 standard deviation blood velocity 28 ± 11 cm/sec; value during ventricular tachycardia 14 ± 8 cm/sec, $P < 0.001$). An "overshoot" of peak blood velocity was observed after ventricular extrasystoles and tachycardia. All such changes in aortocoronary bypass blood velocity related to tachyarrhythmia were more prominent during the systolic fraction of flow. It is concluded that (1) ventricular arrhythmias adversely influence aortocoronary bypass graft function, and (2) this finding supports an aggressive approach to the treatment of these arrhythmias in subjects with bypass grafts.

A previous study from this laboratory[1] demonstrated that phasic instantaneous aortocoronary saphenous vein bypass graft blood velocity can be measured in conscious man by means of a Doppler ultrasonic flowmeter catheter. During that investigation ventricular extrasystoles were found to reduce bypass graft blood velocity in the few patients who experienced them. In this paper we describe in detail the influence of ventricular arrhythmias on phasic aortocoronary graft blood velocity in a larger series of subjects.

Material and Method

Cases: Sixteen patients with 19 saphenous vein bypass grafts constituted the study group. There were 14 men and 2 women aged 42 to 68 (mean 51) years. The anatomic distribution and number of saphenous vein bypass grafts were as follows: right coronary artery 10, left anterior descending coronary artery 8 and left circumflex coronary artery 1. All investigations were incorporated into a routine postoperative evaluation of graft patency and function. Such study was accomplished after a postoperative period of 3 weeks to 2 years. All patients underwent complete left and right heart catheterization with selective coronary arterial and bypass graft cineangiography. Studies were performed with patients in the nonsedated postabsorptive state in the supine position. A right or left medial antecubital vein and the brachial artery were exposed using local anesthesia with 1 percent lidocaine. Intracardiac pressures were measured with saline solution-filled no. 7 or 8 catheters connected to a Statham P23Db strain gauge.

Instantaneous aortocoronary saphenous vein bypass blood velocity: This was measured as previously described[1] using radiotelemetry with a Doppler ultrasonic blood velocity catheter. The catheter was advanced from the brachial artery to the ascending aorta, where graft orifices were identified with metallic clips that had been affixed to the aortic wall at the time of surgery. When the catheter tip was directed to the graft origin, characteristic and reproducible blood

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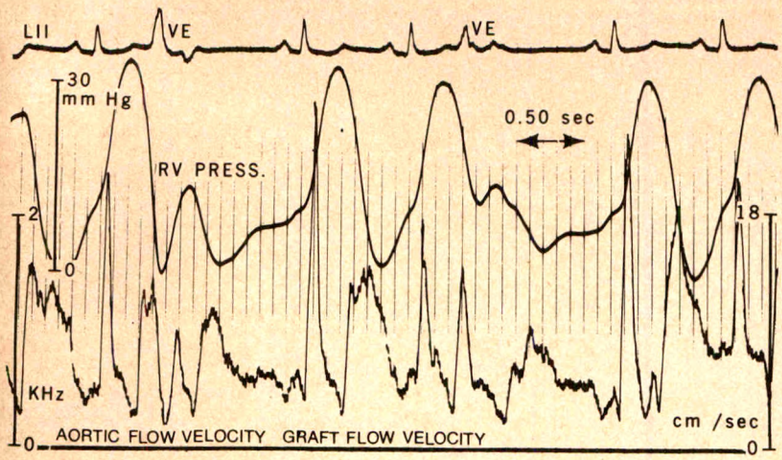


FIGURE 1. Simultaneously recorded lead II (L II) of the electrocardiogram, right ventricular pressure (RV PRESS.) and phasic aortic-right coronary bypass graft blood velocity in a 47 year old man with naturally occurring ventricular extrasystoles (VE). The premature beats produce a 20 to 50 percent reduction in peak diastolic blood velocity and a 60 to 80 percent decrease in peak systolic blood velocity from values during control sinus beats. Postextrasystolic pauses are associated with an "overshoot" of peak bypass graft blood velocities. Note the more prominent alterations in peak systolic blood velocity, arising as a consequence of the arrhythmia.

velocity wave forms were observed. Such bypass blood velocity profiles consist of large systolic and diastolic waves that are distinctly different[1,2] from those recorded in the aorta[3] or at the ostia of native coronary arteries.[4]

To document the validity of the recorded bypass blood velocity wave forms, the ultrasonic catheter tip was advanced within the lumen of the graft under study. The blood velocity wave forms in all such cases were virtually identical to those recorded at the aortocoronary graft orifice. This validation technique has previously been described at length.[1] Systolic blood velocity waves recorded at the origin of and within the bypass graft usually consist of a rapid early systolic upstroke succeeded by smaller mid-late systolic component. This systolic wave contour is dissimilar to that observed in the native coronary artery[4] and is thought to represent the aortic[3] contribution to bypass blood flow in a structure that is not constrained by the ventricular myocardium. Calibration of the Doppler signals has previously been described[1] and is based on earlier descriptions of the method. Each 1 kilohertz of Doppler shift is equivalent to a blood velocity change of 9 cm/sec.

Phasic aortocoronary bypass graft blood velocity was recorded in all 16 subjects during ventricular premature beats; in 11 cases the extrasystoles were evoked by mechanical stimulation of the right ventricular endocardium with the catheter tip. A similar method induced brief episodes of right ventricular tachycardia in 14 patients. In two cases, aortocoronary bypass blood velocity was monitored during naturally occurring paroxysms of wide QRS complex tachyarrhythmia. A total of 19 episodes of ventricular tachycardia were observed in the study group. Control measurements for bypass graft blood velocity during sinus rhythm were obtained by averaging the peak values for 10 consecutive beats. Blood velocity wave forms were likewise measured for all successive beats of venticular tachycardia, and mean levels for systolic and diastolic blood velocities were ascertained.

The audiofrequency signal was continuously monitored with use of a loudspeaker and was recorded on tape. Analog records, right heart pressures, phonocardiograms and lead II of the electrocardiogram were simultaneously recorded on an Electronics for Medicine DR-12 light beam oscilloscopic photographic recorder operated at various paper speeds. Stability of the Doppler catheter tip was observed with fluoroscopic image intensification during the measurement periods to ensure that phasic shifts of blood velocity did not result from major catheter motion.

Results

Ventricular extrasystoles: Premature ventricular depolarizations reduced peak systolic and diastolic graft blood velocities by 20 to 80 percent, generally in relation to their respective coupling intervals. Premature beats preceded by diastolic cycle lengths of less than 0.50 second produced the most marked diminution of bypass graft blood velocity. In all cases, cycle length-dependent

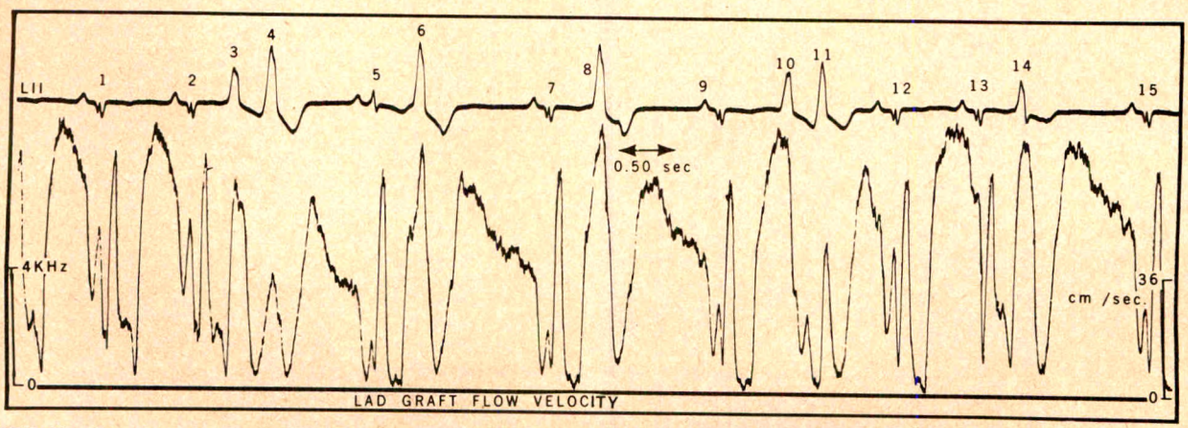


FIGURE 2. Simultaneously recorded lead II (L II) of the electrocardiogram and phasic aortic-left anterior descending (LAD) coronary bypass graft blood velocity in a 45 year old man during catheter-evoked right ventricular premature depolarizations. Paired ventricular extrasystoles (beats 3 to 4, 10 to 11) result in an interectopic loss of diastolic blood velocity.

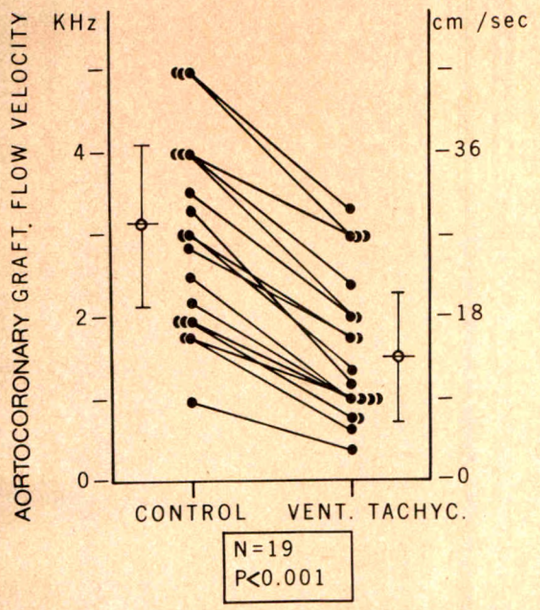


FIGURE 3. Distribution of peak aortocoronary bypass graft blood velocities during sinus rhythm (mean ± 1 standard deviation 28 ± 11 cm/sec) and 19 episodes of ventricular tachycardia (VENT. TACHYC.) (14 ± 8 cm/sec). There is an average 50 percent decrease ($P < 0.001$) in peak blood velocity resulting from this arrhythmia.

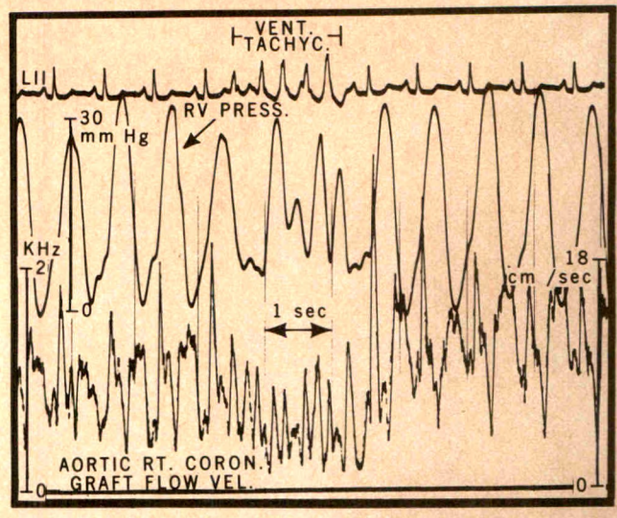


FIGURE 4. Simultaneously recorded lead II (L II) of the electrocardiogram, right ventricular pressure (RV PRESS.) and phasic aortic-right coronary (RT. CORON.) bypass graft blood velocity in a 47 year old man. A paroxysm of ventricular tachycardia (VENT. TACHYC.) produces a maximal 50 percent decrease in peak graft blood velocity (VEL.). The last two beats of the tachyarrhythmia produce an unexpected increase in blood velocity, unrelated to R-R interval prolongation or hemodynamically advantageous P-R intervals. Note the "overshoot" of peak bypass blood velocity recorded during sinus beats that follow termination of the tachycardia.

alterations of blood velocity were more prominent during the systolic fraction and especially so after postextrasystolic pauses that resulted in peak blood velocity "overshoot" (Fig. 1). Diastolic bypass blood velocity times were curtailed in direct relation to shortened R-R intervals, and when ventricular extrasystoles occurred close together in salvos there was a virtual cessation of the phasic diastolic component (Fig. 2).

Ventricular tachycardia: Ventricular tachycardia effected profound reductions of peak aortocoronary bypass blood velocity, and the records became completely irregular. The tachyarrhythmia ranged from 100 to 170/min, and the most prominent reduction in peak blood velocity levels was noted during paroxysms exceeding 130/min. The 19 transient episodes of ventricular tachycardia produced an average 50 percent reduction in bypass graft blood velocity (control mean ± 1 standard deviation blood velocity 28 ± 11 cm/sec; blood velocity during ventricular tachycardia 14 ± 8 cm/sec, $P < 0.001$ (Fig. 3). In 8 of 19 documented episodes of ventricular tachycardia there was an unexpected increase in peak bypass graft blood velocity just before the arrhythmia terminated. This augmentation of phasic blood velocity was not dependent on longer R-R intervals or hemodynamically advantageous P-R interval changes during ventricular tachycardia. In 14 of 16 subjects, termination of the tachycardia was associated with a marked "overshoot" of peak systolic and diastolic blood velocities during the first three to eight succeeding sinus beats (Fig. 4). This "overshoot" phenomenon was observed only after resumption of the patient's basic rhythm. Longer R-R intervals occurring after the last beat of tachycardia were associated with a sustained decrease in diastolic blood velocity (Fig. 5). No patient experienced angina pectoris during these short periods of ventricular arrhythmia.

Discussion

Our findings represent the first comprehensive description of aortocoronary bypass graft blood velocity during ventricular arrhythmias in man. Previous investigation has demonstrated substantial reductions in peak phasic aortic[5,6] and native coronary[7] arterial blood velocities during such arrhythmias. It can be surmised that reduced stroke output, shortened blood velocity times and diminished ejection of blood into the aorta were factors responsible for the adverse influence of ventricular arrhythmias on bypass graft blood velocity. Ventricular extrasystolic coupling intervals shorter than 0.50 second have also been noted uniformly to reduce peak native coronary arterial blood velocity in human subjects.[8] Additionally, the finding that tachycardias exceeding 130/min produced the most prominent reduction in bypass blood velocity is in accord with the range of critical rates (120 to 150/min) required for a substantial reduction of coronary flow velocity during ventricular tachycardia.[7]

The increase in aortocoronary blood velocity after ventricular extrasystoles and tachycardia probably represents a form of postextrasystolic potentiation and is similar to blood velocity profiles at other anatomic sites after these arrhythmias.[6] The basis for augmentation of peak blood velocity during ventricular tachycardia, unrelated to prolongation of cycle length or hemodynamically favorable P-R intervals, is incompletely understood[6] and warrants further investigation.

Bypass graft versus native coronary arterial blood velocity responses: Despite the similarities

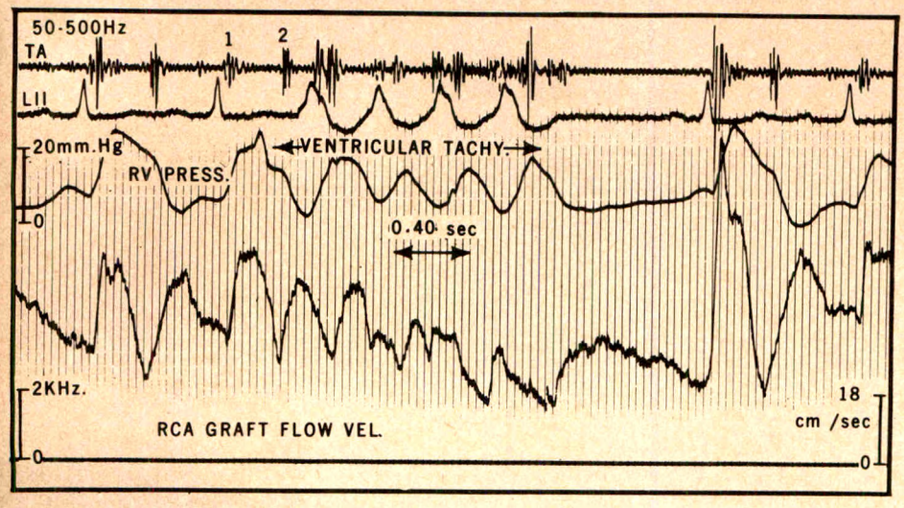


FIGURE 5. Simultaneously recorded tricuspid area (TA) phonocardiogram, lead II (L II) electrocardiogram, right ventricular (RV) pressure (PRESS.) and aortic-right coronary artery bypass blood velocity (VEL.) in a 65 year old man with a 4 beat burst of ventricular tachycardia (TACHY.). The arrhythmia produces a progressive decline of phasic bypass graft blood velocity. Note the reduced diastolic blood velocity level which follows cessation of the tachycardia and before the first sinus beat.

between the phasic instantaneous diastolic blood velocity response to ventricular arrhythmias noted in the native coronary arterial system and in the bypass graft, the systolic changes were distinctly different. Cycle length-dependent variations of peak systolic blood velocity were uniformly greater at the origin of the bypass graft and particularly during the "overshoot" after premature ventricular depolarizations and ventricular tachycardia. These systolic responses were reminiscent of the marked changes in peak blood velocity observed in the aortic root during cardiac arrhythmias.[3] It is therefore apparent that ventricular arrhythmias alter the bypass graft systolic blood velocity profile in a manner akin to that noted in the aorta whereas diastolic events resemble those seen in the native coronary arterial system. Initial study of bypass blood velocity wave forms indicated that this major systolic fraction was characteristic of graft flow and could not be ascribed to aortic blood velocity "contamination" of the sensing crystal of the catheter tip.[1] The underlying cause of this difference between native coronary arterial and graft blood velocity characteristics is unknown but it may be related to hemodynamic influence of the sinuses of Valsalva or major bidirectional systolic blood velocities within the saphenous vein bypass graft segment.

Limitations of study: The limitations of studies of this kind have previously been described in detail. The wave forms described herein represent unidirectional blood velocity and not volumetric flow. We contend that reductions in peak blood velocity at the origin of and within the bypass grafts during ventricular arrhythmias are strong indications of reduced myocardial perfusion. It is now impossible to measure directly the luminal circumference of the bypass graft while simultaneously estimating phasic blood velocity in closed chest human subjects. A maintenance of volumetric flow concomitant with reduced blood velocity could be attributed to dilation of the bypass graft lumen during arrhythmias. Aortographic study indicates that there is negligible variation in graft circumferential size under these conditions.[1] These considerations provide strong indirect proof that blood velocity in part reflects flow within the saphenous vein segment.

Clinical implications: Despite its drawbacks, the Doppler ultrasonic flowmeter technique is the only method for directly measuring some aspects of phasic blood flow within the aortocoronary grafts of conscious man. The clinical implications of these findings are clear. An aggressive approach to the treatment of ventricular arrhythmias appears to be indicated in subjects with bypass grafts since these rhythm disturbances have a decidedly adverse influence on the blood transport function of these grafts.

Acknowledgment

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Structural Changes in Porcine Xenografts Used as Substitute Cardiac Valves

Gross and Histologic Observations in 51 Glutaraldehyde-Preserved Hancock Valves in 41 Patients

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Gross and histologic changes are described in 51 Hancock glutaraldehyde-preserved porcine heterograft bioprostheses from 41 patients: 33 valves from 25 patients had been in place for less than 2 months ("early") and 18 valves from 17 patients were examined at later periods up to 75 months ("late") after implantation. The major gross changes were thrombosis (five bioprostheses) and degeneration (three bioprotheses) of the cusps. Major histologic changes observed in 44 bioprostheses (26 early and 18 late) examined histologically were: (1) fibrin deposits on inflow and outflow surfaces of the cusps; (2) inflammatory cell infiltrates; (3) histiocyte deposition; (4) giant cell formation, and (5) focal disruption of the fibrocollagenous structure of the cusps. These observations indicate that porcine bioprostheses are not biologically inert in the human circulation. However, valve failure is rare at the implantation periods studied.

The glutaraldehyde-preserved stented porcine xenograft is now widely used as a substitute cardiac valve,[1–10] yet relatively little information is available on structural changes in this bioprosthesis.[3–10] This report describes gross and histologic observations in 51 Hancock glutaraldehyde-preserved porcine cardiac valve bioprostheses (Hancock Laboratories, Anaheim, California) from 41 patients whose bioprostheses had been in place for up to 75 months.

Materials and Methods

Of the 51 valves, 47 were examined at necropsy in 38 patients; 33 valves from 25 patients (10 men and 15 women) had been in place for less than 2 months ("early") (range 0 to 50 days, mean 12) and 18 valves from 17 patients (8 men and 9 women) were examined more than 2 months ("late") after implantation (range 2.1 to 75 months, mean 15). Seven of the 18 late valves had been in place for longer than 12 months. Each bioprosthesis was fixed in either 10 percent buffered formalin or 3 percent glutaraldehyde. In 44 of the 51 valves a section was taken for histologic examination from each of the three cusps. The sections were processed in alcohols and xylene, embedded in paraffin, cut and stained. One section from each cusp was stained by the hematoxylin-eosin, Verhoeff-van Gieson, calcium, phosphotungstic-acid hematoxylin and Movat's pentachrome methods. Each section was examined with both light and polarization microscopy.

Of the 33 early valves, 19 were in the mitral position and they ranged in size from 25 to 35 mm (average 29 mm), 10 were in the tricuspid position (range 29 to 35 mm, average 33 mm), 3 were in the aortic position (27, 27 and 29 mm, respectively) and 1 was in the pulmonary position (21 mm) as part of a composite conduit.

Of the 18 late valves, 12 were in the mitral position (size range 25 to 35 mm, average 29 mm), 5 in the tricuspid position (31 to 35 mm, average 33 mm) and 1 was in the aortic position (25 mm). Four valves (three mitral and one tricuspid) were removed at operation because of prosthetic regurgitation caused in three

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TABLE I

Prosthetic Dysfunction or Prosthesis-Related Complications

Type of Dysfunction	no.	Affected Bioprostheses	
		Valve Site	Duration of Implantation
Leaflet degeneration (regurgitation)	3	Mitral	56 months
		Mitral	75 months
		Tricuspid	3 months
Thrombosis (stenosis)	5	Mitral and tricuspid	32 days
		Mitral	8 days
		Aortic	5 months
		Tricuspid	2 months
Strut in outflow tract	3	Mitral	1 day
		Mitral	4 days
		Mitral	6 days
Prosthetic disproportion	3	Tricuspid and mitral	4 days
		Aortic	1 day
Coronary ostial obstruction	1	Aortic	1 day

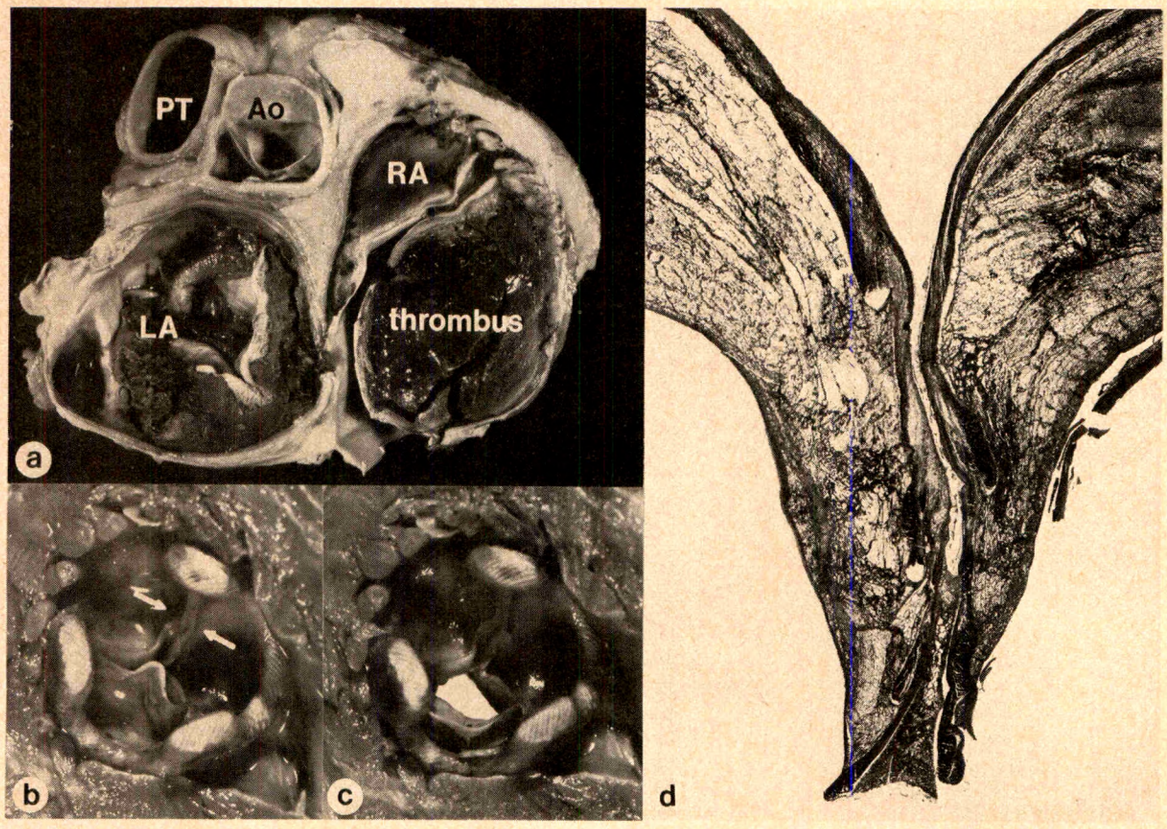


FIGURE 1. Stenosis of porcine bioprostheses implanted 32 days earlier in a 61 year old woman who had had rheumatic mitral stenosis and tricuspid regurgitation. The patient sustained an air embolus intraoperatively and remained comatose with severe low cardiac output after operation. **a,** at necropsy, both the right (RA) and left (LA) atria were filled with organizing thrombi. Ao = aortic root; PT = pulmonary trunk. **b,** view of the 31 mm porcine bioprosthesis in the tricuspid position from the ventricular aspect as seen in systole. Thrombus is present in two of the three cusp sinuses and there is fusion of the commissure between these leaflets **(arrows). c,** bioprosthesis in simulated ventricular diastole. The fusion of two leaflets permits opening of only the one mobile leaflet with resulting valve stenosis. **d,** section through fused leaflets at level of arrows in **b** showing adherence of the leaflets by fibrin thrombus. (Phosphotungstic acid-hematoxylin stain ×16, reduced by 24 percent [**d**].)

by prosthetic degeneration and in the fourth by a parabasilar leak. The two mitral valves with the longest implantation time (56 and 75 months, respectively) were removed because of severe regurgitation secondary to leaflet degeneration; at reoperation, these two valves were replaced with fresh Hancock xenografts. One of these two patients died 14 days later of respiratory complications.

Results

Gross Observations

Of the 33 bioprostheses with implantation periods of less than 2 months, 30 were entirely normal on visual inspection at necropsy, and the remaining 3 showed some gross alterations (discussed later). Of the 18 bioprostheses implanted for more than 2 months, 13 were normal on visual inspection at necropsy, and the remaining 5 showed some gross alteration either at necropsy or reoperation. The major gross changes observed in these eight bioprostheses included thrombosis (both early and late) and degeneration (late only) of the cusps (Table I).

Cusp thrombus: This was present in five bioprostheses (two mitral, two triscuspid and one aortic). Bioprostheses were implanted in both the mitral and

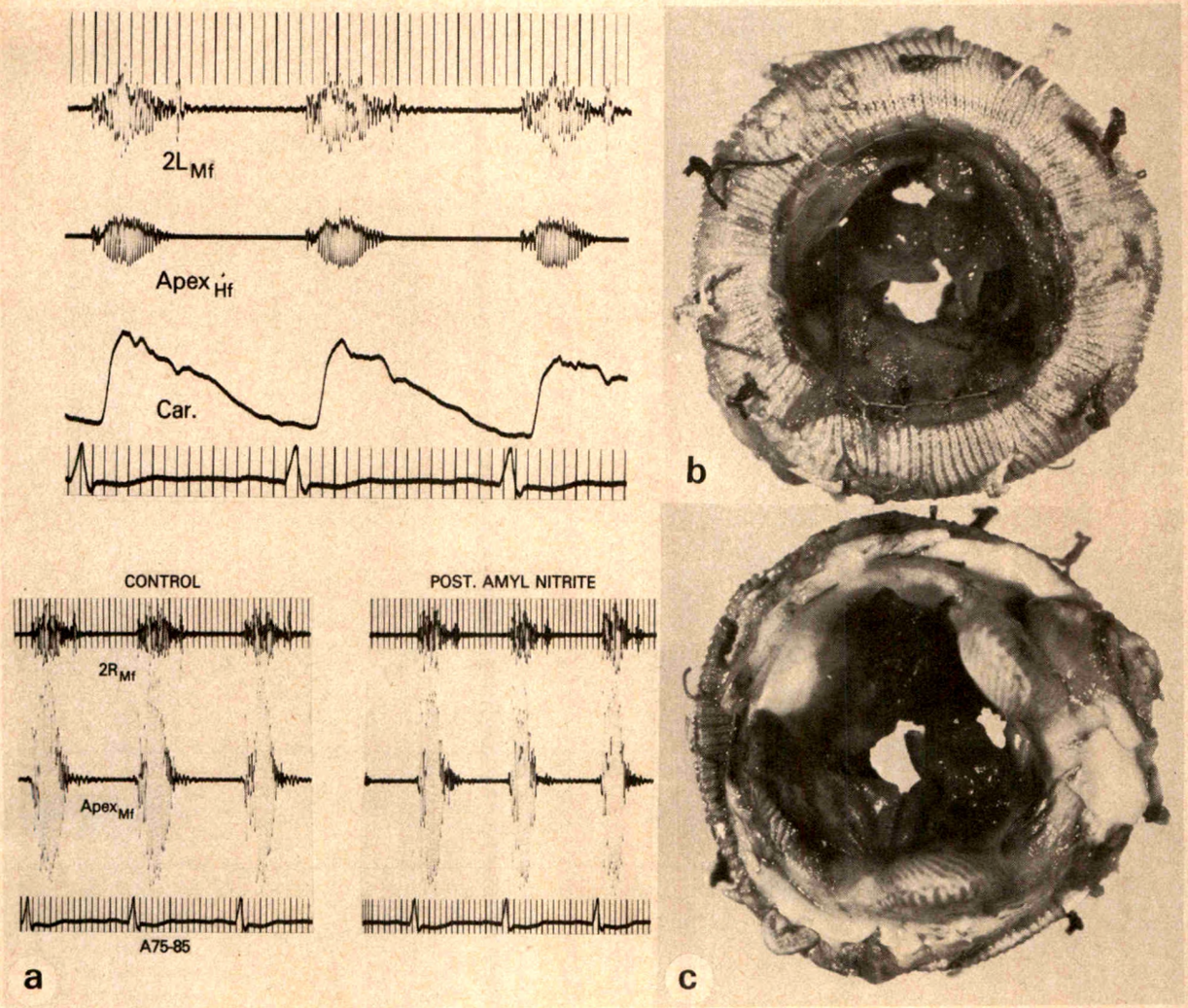


FIGURE 2. Tissue degeneration in a 56 month old porcine bioprosthesis in the mitral position. The patient had undergone mitral valve replacement and aortic and tricuspid valve commissurotomy for mitral, aortic and tricuspid stenosis. She did well for 56 months (without anticoagulant therapy) when she had the sudden onset of left-sided chest pain and dyspnea, and a murmur of mitral regurgitation was heard for the first time postoperatively. At no time was evidence for infective endocarditis present. Phonocardiograms **(a)** now showed a systolic precordial murmur consistent with mitral regurgitation (no increase with amyl nitrite). Cardiac catheterization revealed 4+/4+ mitral regurgitation, and at reoperation the 29 mm porcine mitral bioprosthesis **(b,c)** showed extensive disruption of the leaflets and adherent thrombotic material. At reoperation, the porcine mitral valve was replaced with a new porcine bioprosthesis. The tricuspid valve, which was stenotic, also was replaced with a porcine bioprosthesis, and the aortic valve, which was both stenotic and regurgitant, was replaced with a size 7A, model 2320 Starr-Edwards prosthesis. The patient did well for the first 2 weeks postoperatively but experienced sudden chest pain on the 14th postoperative day and died.

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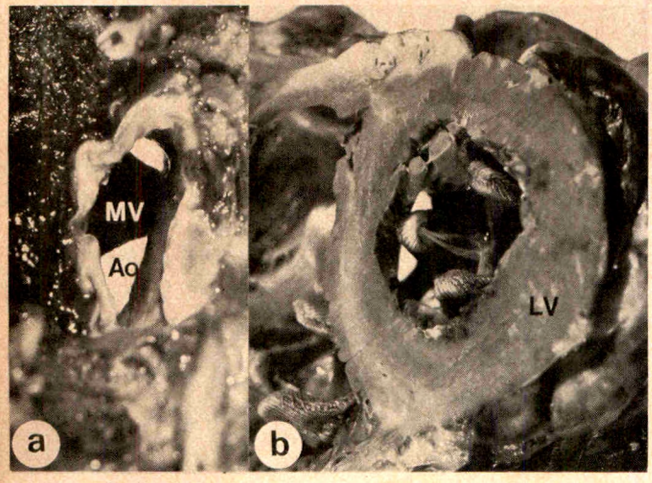


FIGURE 3. Strut of porcine bioprosthesis in the mitral position partially obstructing left ventricular (LV) outflow in a 54 year old woman who had undergone tricuspid and mitral valve (MV) replacement with mechanical prostheses for valve stenosis 3 days before death. She had a low cardiac output requiring pressor agents postoperatively. The prosthetic valve sounds were poorly heard and reexploration performed on the third postoperative day revealed that the mechanical tricuspid prosthesis had thrombosed. Both mechanical prostheses in the tricuspid and mitral positions were replaced with porcine bioprostheses, but the patient could not be separated from cardiopulmonary bypass. At necropsy, one strut of the mitral prosthesis partially obstructed left ventricular outflow **(a). b,** ventricular aspect, showing placement of the porcine valve strut in the outflow tract.

tricuspid valve positions in one patient, who died 32 days postoperatively after a prolonged period of inadequate cardiac output (Fig. 1). At necropsy, thrombus filled the sinuses of two of the three cusps of the tricuspid valve prosthesis, and one of the three commissures had fused; only one of the three cusps remained pliable and consequently the prosthetic orifice appeared stenotic. The bioprosthesis in the mitral position in the same patient also contained thrombus in two of the three cusps, but none of the commissures had fused. Both atria at necropsy were filled with organizing thrombus. In a second patient with a bioprosthesis in the mitral position, a large thrombus, which filled the body and appendage of the left atrium, was attached to the atrial aspects of each of the three cusps; in addition, thrombus also filled the sinus portions of each of the

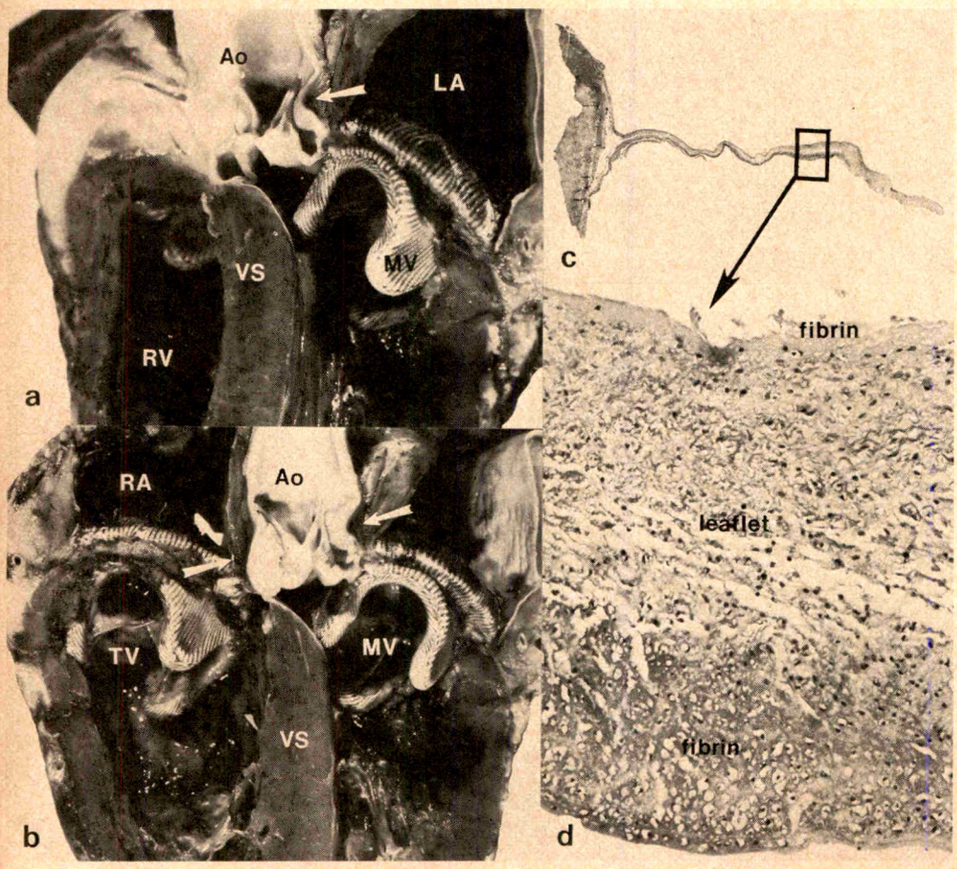


FIGURE 4. Prosthetic disproportion in a 50 year old woman who had had mitral (MV) and tricuspid (TV) valve replacements with porcine bioprostheses 4 days before death for mitral and tricuspid valve stenosis. She was in a low cardiac output state despite vasopressors during the entire postoperative period. At necropsy, one strut of the mitral bioprosthesis partially obstructed left ventricular outflow. In addition, the sewing ring of the 31 mm bioprosthesis in the mitral position appeared to indent the aorta (Ao) just above the valve **(arrow) (a). b,** the 31 mm bioprosthesis in the tricuspid valve position also compressed **(arrow)** the aortic root, possibly causing some aortic regurgitation. At necropsy, thrombus was present in the left atrium (LA). RA = right atrium; RV = right ventricle; VS = ventricular septum. **c,** section of one leaflet of the bioprosthesis in the mitral position showing fibrin deposits. **d,** higher power view of area enclosed by the box in **c,** showing fibrin on both surfaces. (Hematoxylin-eosin stains ×6.5 **[c]** and ×220 **[d],** reduced by 30 percent.)

three cusps, thereby producing severe prosthetic obstruction. This patient lived 8 days postoperatively and the cause of the thrombosis was not determined. One bioprosthesis in the tricuspid valve position for 2 months had gross thrombi in the cusps with only mild limitation of movement of the leaflets. In one bioprosthesis in the aortic valve position for 5 months, thrombus was present in two of the three sinuses.

Clinical or morphologic evidence for thromboembolism was present in four patients with late bioprostheses, but all four patients had mechanical prostheses in addition to porcine bioprostheses, and three had thrombus present on the mechanical prostheses. In one patient who had a 31 mm tricuspid valve bioprosthesis implanted 21 months earlier, evidence of pulmonary embolism occurred 3 months postoperatively. The origin of the embolus is unclear, but at necropsy fibrin thrombus was present in the sinuses of the bioprosthesis although she had had long-term warfarin sodium therapy.

Cusp degeneration: Degeneration of the cusp tissue with resulting regurgitation was present in three valves, two mitral (with an implantation period of 56 and 75 months, respectively) (Fig. 2) and one tricuspid valve with a 3 month implantation period. All three bioprostheses showed tears of the cusps with adherent thrombus. In the 56 and 75 month old mitral bioprostheses, gross nodular calcific deposits were present.

In three mitral valves, one of the three struts of the flexible stent was in the left ventricular outflow tract (Fig. 3). All three patients were hypotensive throughout the postoperative period and died 1, 4 and 6 days, respectively, after operation.

Prosthetic disproportion: This was present in two patients (three valves). In one, a woman with tricuspid regurgitation and severe mitral stenosis, 31 mm mitral and 33 mm tricuspid valve prostheses were implanted. Postoperatively, she had evidence of inadequate cardiac output and, finally, complete heart block. At necropsy (Fig. 4), the sewing rings of the prostheses compressed the aortic root. In the second patient, the struts of an aortic bioprosthesis obstructed both coronary ostia; this patient died soon after operation from circumferential myocardial necrosis (Fig. 5).

Fatal endocarditis was present on a mechanical prosthesis in two patients (aortic in one and mitral in one), but the porcine bioprostheses (mitral and tricuspid, respectively) were uninvolved (Fig. 6).

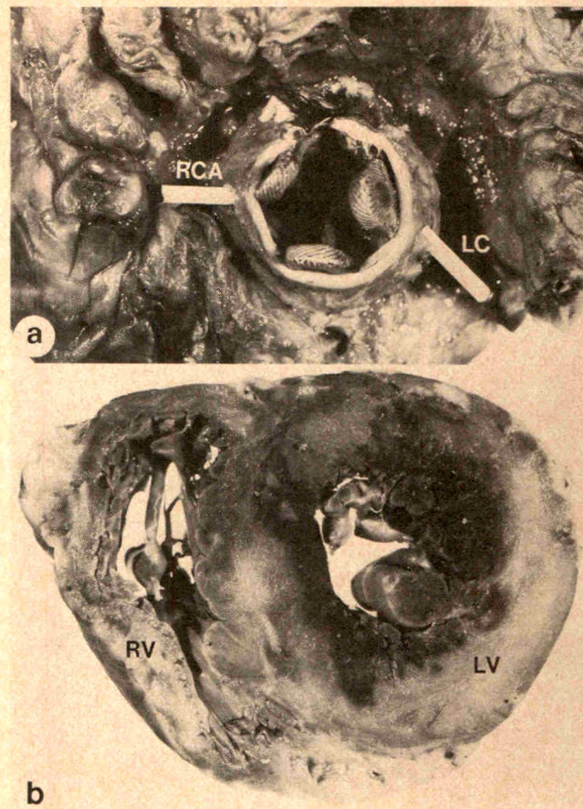


FIGURE 5. Coronary ostial occlusion by a 27 mm porcine bioprosthesis in the aortic position in a 63 year old woman who had had aortic stenosis. The patient died with pulmonary edema 36 hours after operation. **a,** view of aortic prosthesis from above. A Teflon® patch was used to attempt to widen the aorta. White sticks designate the origins of the right (RCA) and left main (LC) coronary arteries. The origins of both major coronary arteries are occluded by the struts of the prosthesis. **b,** section of ventricles showing extensive circumferential hemorrhagic necrosis. LV = left and RV = right ventricle.

Histologic Observations

Of the 51 porcine bioprostheses, 44 were examined histologically (Table II). In addition, two unimplanted glutaraldehyde-fixed porcine valves were sectioned to

TABLE II

Histologic Findings in 44 Porcine Xenograft Cardiac Valve Bioprostheses

	Fibrin in Cusps*		Fibrin on Inflow Surface†		WBC‡		Histiocytes		Giant Cells		Leaflet Disruption§	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
Early (no. = 26)	18	69	12	46	16	62	14	54	7	27	4	15
Late (no. = 18)	14	78	9	50	13	72	14	78	12	67	8	45

* Ventricular surface of tricuspid and mitral valves; aortic surface of aortic valves.
† Atrial surface of tricuspid and mitral valves, ventricular surface of aortic valves.
‡ Plasma cells, polymorphonuclear leukocytes, lymphocytes.
§ Focal invasion of leaflets by host cells or disruption.

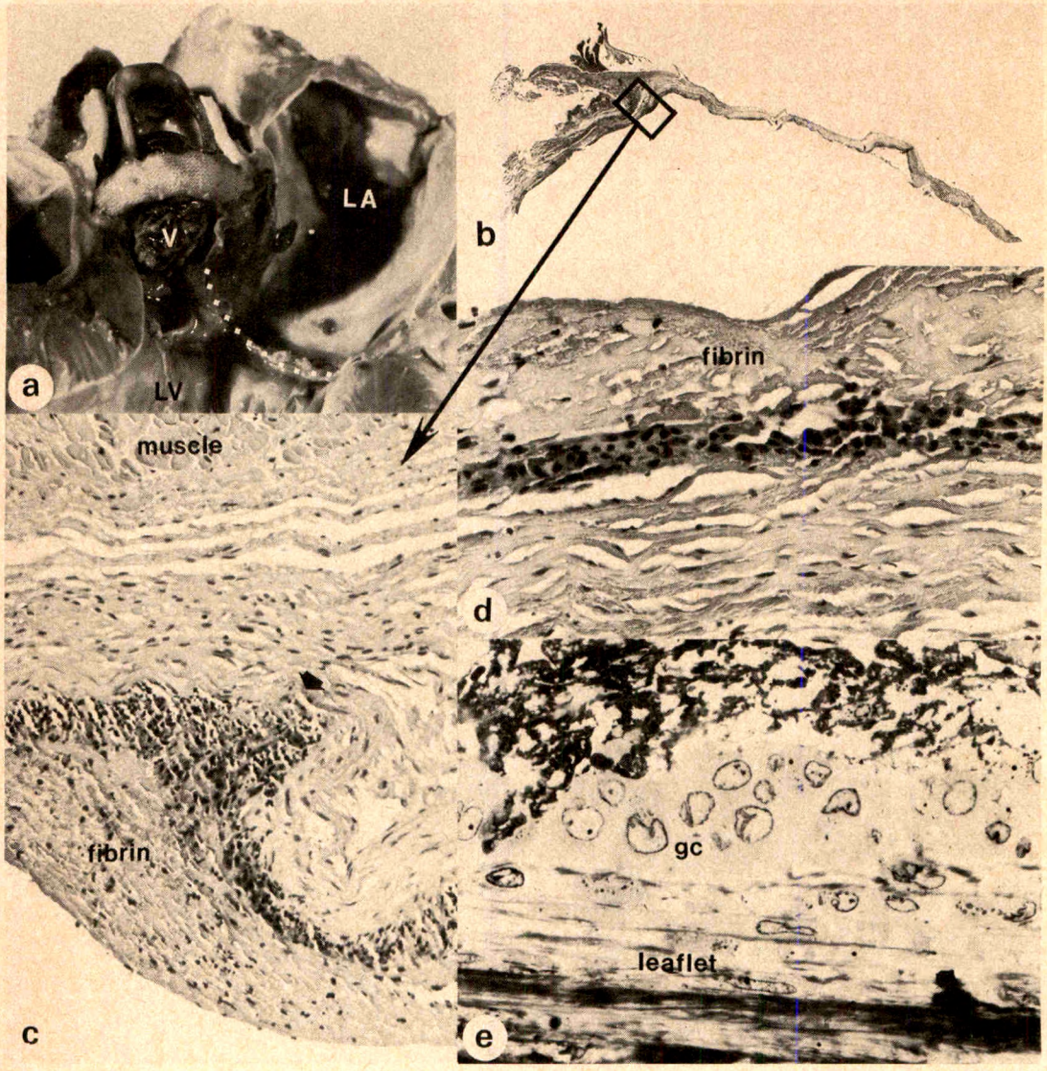


FIGURE 6. Staphylococcus epidermidis endocarditis on a mechanical prosthesis implanted 28 days before death in a 47 year old man with aortic and mitral regurgitation and replacement of the mitral valve with a porcine bioprosthesis. The patient received warfarin daily postoperatively. **a,** view of mechanical aortic valve prosthesis showing obstruction of the primary orifice by vegetations (V). The anulus of the mitral valve prosthesis **(dotted line)** is designated. LA = left atrium; LV = left ventricle. **b,** section of one leaflet of the removed bioprosthesis in the mitral position showing intact leaflet structure. **c,** area enclosed by box in **b** near hinge of leaflet showing fibrin and inflammatory cell deposition with focal invasion of the valve tissue **(arrow). d,** high power view of the atrial surface of the leaflet showing fibrin and inflammatory cell deposition. **e,** thin section of surface of the leaflet showing giant cells (gc) and histiocytes under a fibrin layer. Stains for bacteria and fungi did not reveal infection of the tissue valve. (Hematoxylin-eosin stains ×7.5 **[b],** ×220 **[c],** ×350 **[d]** and toluidine blue stain ×860 **[e],** all reduced by 21 percent.)



FIGURE 7. Normal unprocessed and unimplanted porcine valve. Bundles of fibrocollagenous tissue within a matrix of ground substance are present. Cells with elongated nuclei are scattered throughout the leaflet. Thin delicate endothelium is present on one surface. (Hematoxylin-eosin stain ×220, reduced by 28 percent.)

serve as controls.* Of the three cusps in the normal porcine aortic valve, the right one is attached to a "muscle shelf" that consequently limits the pliability of this cusp.[11] Each of the three cusps is composed of multiple layers of cells with elongated nuclei, collagen bundles arranged radially and short elastic fibers (Fig. 7).

"Early" valves: Of the 33 valves with implantation periods of less than 2 months, 26 were examined histologically. *Fibrin deposits* were present on the outflow surfaces of the cusps in 18 (69 percent) (Fig. 4), and on the inflow surfaces of 12 (46 percent) bioprostheses. Occasionally, the fibrin deposits were large enough to limit cusp mobility (Fig. 1). Collections of platelets and erythrocytes were associated with the fibrin deposits in a few patients. Three patients whose bioprostheses had been implanted for 13, 14 and 19 days, respectively, received warfarin daily postoperatively. Two of the three valves from these patients showed moderate fibrin deposits on the cusps of the bioprostheses. Leukocytes, lymphocytes and, occasionally, plasma cells were

* Courtesy of Warren D. Hancock, Hancock Laboratories, Anaheim, California.

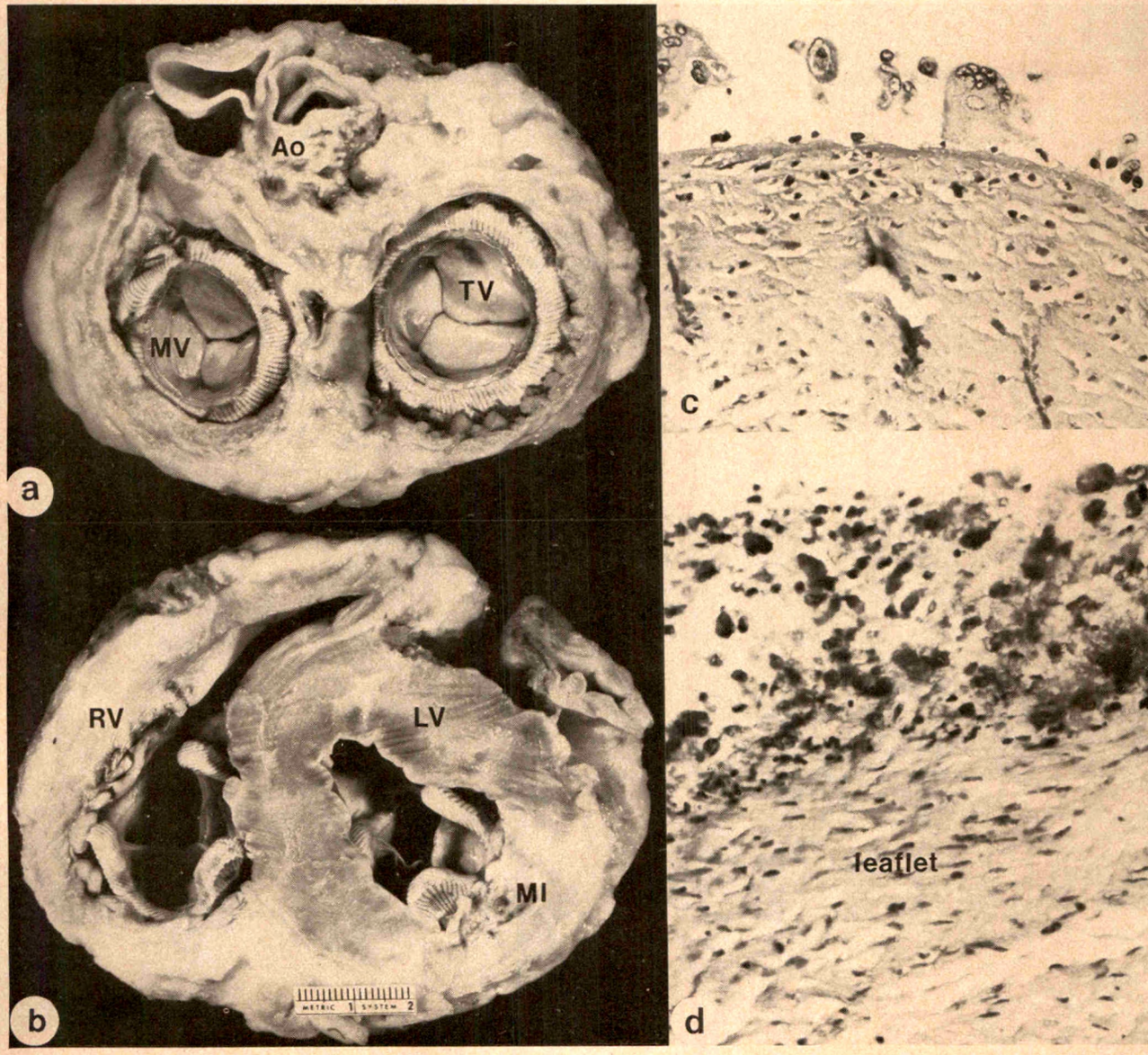


FIGURE 8. Same patient as in Figure 3. The porcine bioprostheses in the mitral and tricuspid valve positions had been implanted 14 days earlier. Postoperatively, the function of both bioprostheses was normal. **a,** view from above showing the tricuspid (TV), mitral (MV) and aortic (Starr-Edwards) (Ao) prostheses. **b,** view from below showing posterobasal transmural myocardial infarct (MI) of the left ventricle (LV). RV = right ventricle. **c,** section of one leaflet of the 14 day old bioprosthesis in the mitral position. Marked giant cell reaction and a few lymphocytes and plasma cells line the surface of the leaflet. **d,** section of one leaflet of the bioprosthesis in the tricuspid valve position. Histiocytes, inflammatory cells and fibrin cover the leaflet's surface, and its interior is invaded by the inflammatory cells. (Hematoxylin-eosin stains [**c** and **d**], ×330, reduced by 17 percent.)

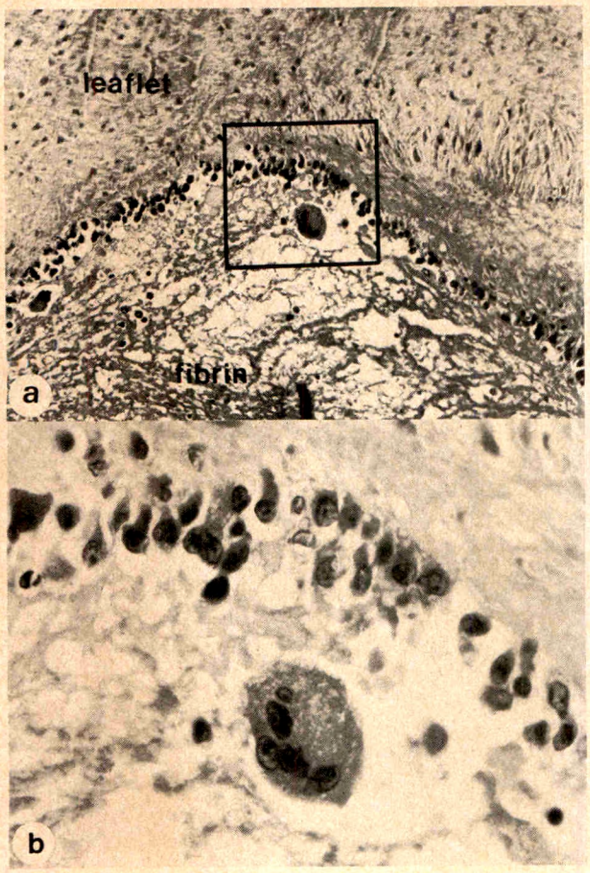
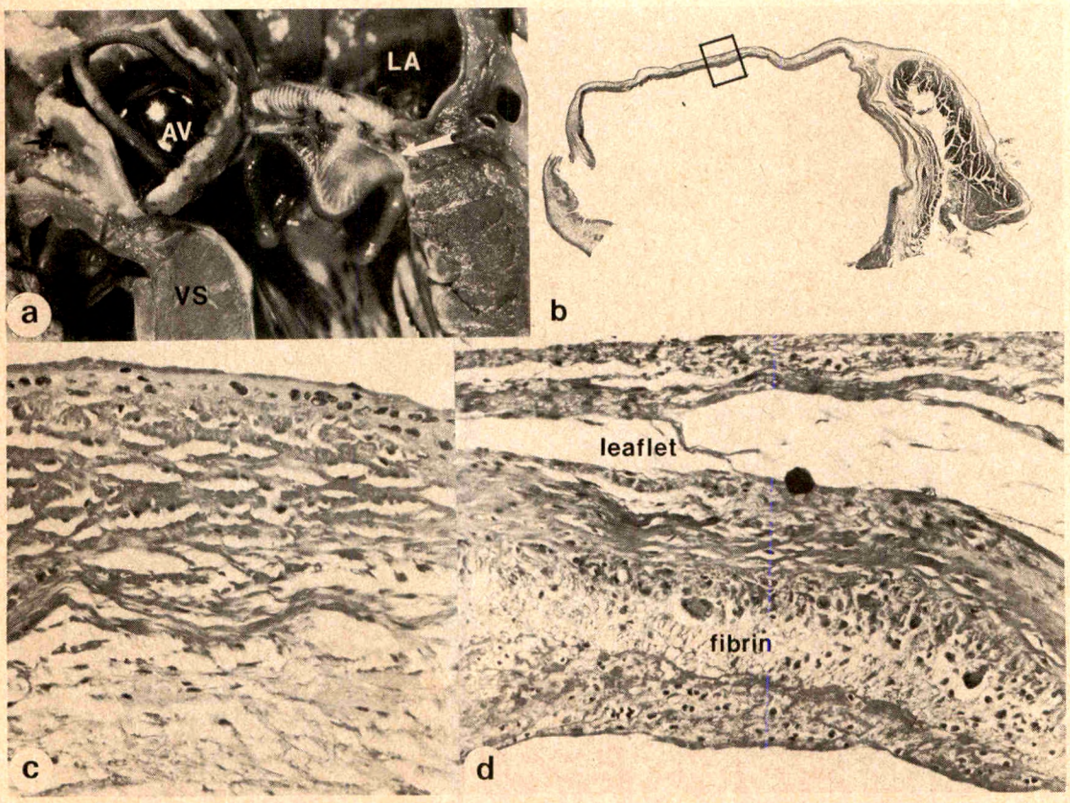


FIGURE 9 (left). Histiocyte, giant cell and inflammatory cell reaction in the cusp of a bioprosthesis in the mitral position. It had been implanted 7 months earlier. **a,** closeup of area enclosed by the box in **a** is shown in **b.** A large giant cell is present in the fibrin matrix. (Hematoxylin-eosin stains ×220 **[a]** and ×860 **[b],** reduced by 28 percent.)

FIGURE 10 (below). Porcine bioprosthesis in the mitral position implanted 14 months earlier. **a,** longitudinal view of heart showing moderate host tissue overgrowth on the struts of the bioprosthesis **(arrow),** and the relation of the bioprosthesis to the mechanical prosthesis in the aortic valve (AV) position. LA = left atrium; VS = ventricular septum. **b,** section of one leaflet of the bioprosthesis showing a thin, delicate leaflet. **c** and **d,** higher-power view of area enclosed by box in **b. c,** atrial side; a thin fibrin layer with histiocytic cells lines the surface of the leaflet. Little nuclear staining of the glutaraldehyde-fixed porcine leaflet cells is present. **d,** ventricular side; a thick fibrin coat with enclosed giant cells, plasma cells and histiocytes is present with mild surface invasion of the leaflet. (Hematoxylin-eosin stains ×8 **[b],** ×330 **[c],** ×350 **[d],** reduced by 24 percent.)



present in the fibrin matrix or along the leaflet surface in 16 (62 percent) of the 26 bioprostheses. Often leukocytes infiltrated the porcine aortic wall behind the cusps.

Macrophages with histologic characteristics of histiocytes lined portions of the cusps in 14 (54 percent) of the 26 bioprostheses, and in 7 of the 14 valves histiocytes had collected together forming giant cells. The histiocytes occasionally were present in the outermost portions of the fibrocollagenous structure of the cusps. On polarization microscopy, talc and other foreign bodies were absent. Of the seven bioprostheses that showed a giant cell reaction, giant cells were present in small numbers in three patients with bioprostheses in place for less than 30 days, whereas in the three patients with bioprostheses in place from 30 to 60 days, they were present in abundance. In one patient, two bioprostheses (one mitral, one tricuspid), each in place for 14 days, showed marked inflammatory cell reaction, histiocyte accumulation and giant cell formation (Fig. 8). In this patient a 56 month old bioprosthesis was removed from the mitral position because disruption of the cusps had resulted in regurgitation. The mitral and tricuspid valves were then replaced with fresh bioprostheses. In 4 (15 percent) of 26 bioprostheses, the substance of the cusps contained inflammatory cells or histiocytes. However, none of these four bioprostheses showed either clinical or necropsy evidence of dysfunction.

The fibrocollagenous structure of the remaining 22 bioprostheses was intact and appeared unchanged from the structure of the 2 control valves. Despite good ingrowth of tissue over the struts and the sewing rings of the prostheses, host cell ingrowth was absent on the leaflet surfaces of all bioprostheses in place for less than 2 months. Host cell ingrowth extended only a few millimeters beyond the sewing ring over the porcine tissue.

"Late" valves: All 18 valves that had been in place for more than 2 months were available for histologic study (Table II). *Fibrin deposits* were present on the

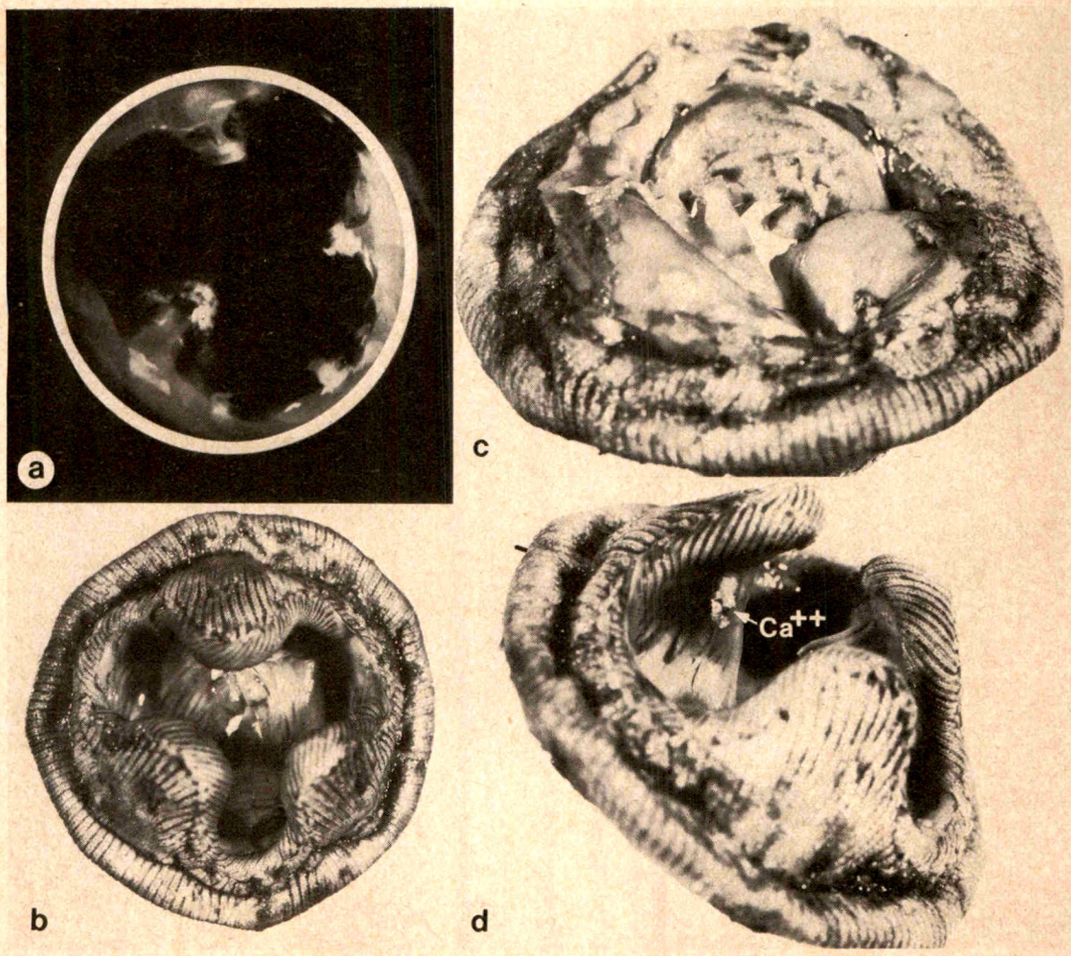


FIGURE 11. Tissue degeneration and calcification in a 75 month old porcine bioprosthesis that had been in the mitral position. **a,** roentgenogram of the removed bioprosthesis showing focal calcific deposits in the leaflets. **b,** view of the bioprosthesis from the ventricular aspect showing bowing-in of all three struts. **c,** view of the bioprosthesis from the atrial aspect showing tears and fraying of two of the three leaflets and prolapse of the leaflets toward the atrial side of the valve. The resulting regurgitation required reoperation and replacement of the bioprosthesis with a fresh bioprosthesis. **d,** side view showing nodular calcific deposits (Ca^{++}) at the commissural attachment of two leaflets.

outflow surface of the cusps in 14 (78 percent) of the 18 bioprostheses and on the inflow surface in 9 (50 percent). *Leukocytes* were present in 13 bioprostheses (72 percent) and *histiocytes* lined the cusp surfaces in 14 (78 percent). *Giant cell* formation was frequent (Fig. 9); 12 (67 percent) showed giant cells, and focal invasion of the cusps by host cells and giant cells was present in 8 (45 percent) (Fig. 10). In three valves, a 3 month old tricuspid and two much later (56 and 75 months, respectively) mitral valves, complete disruption of cusp tissue occurred (Fig. 2). The two mitral valves also had calcific deposits in the cusps (Fig. 11). Except for a few giant cells, cell elements were absent and collagen was degenerated in these two bioprostheses.

Marked host cell endothelialization of the cusps was observed in one bioprosthesis in place in the tricuspid position for 21 months (Fig. 12); however, the endothelial cells were present over a thin layer of fibrin and

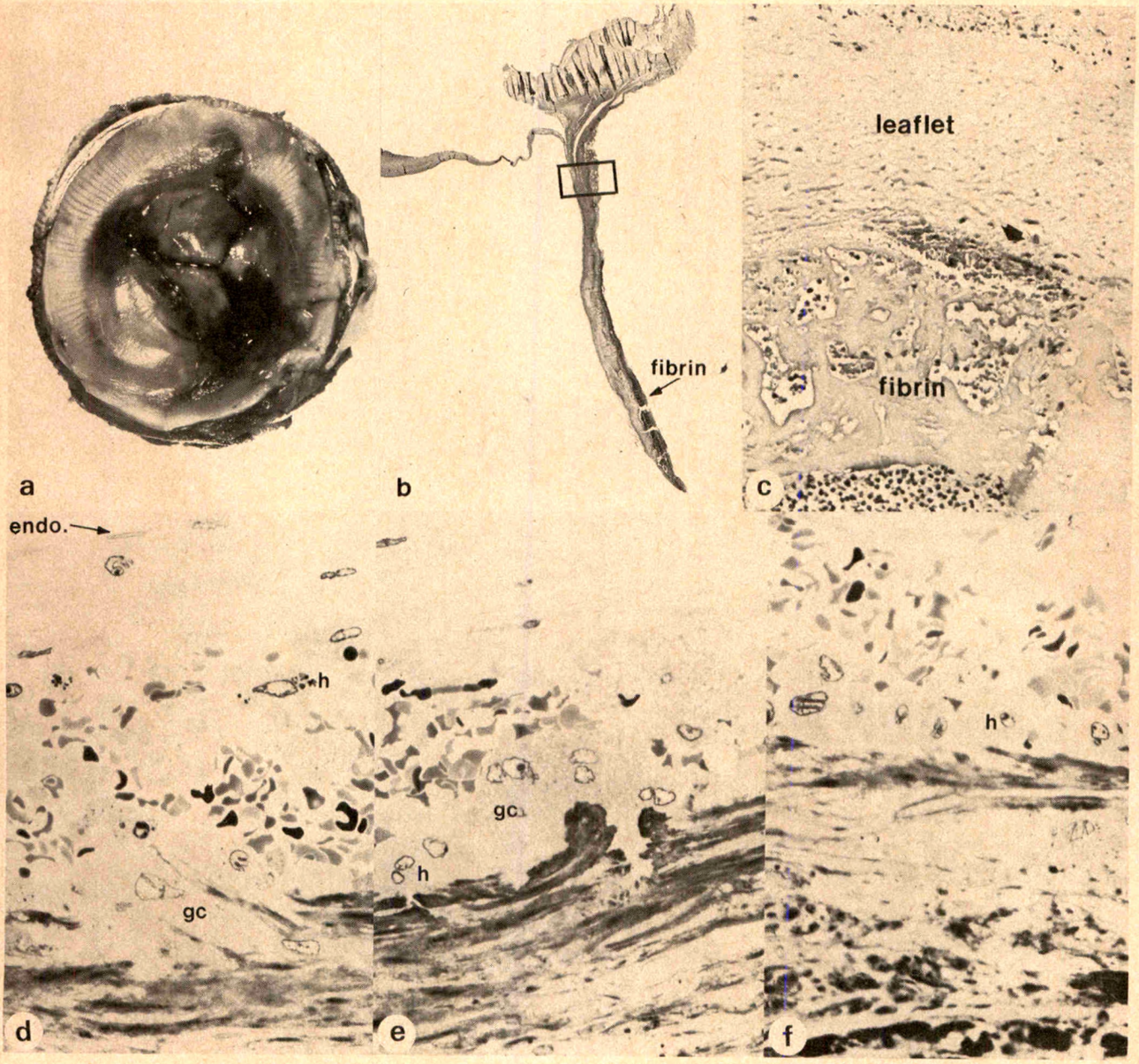


FIGURE 12. A 31 mm bioprosthesis that was in the tricuspid valve position for 21 months in a 57 year old woman who also had Starr-Edwards aortic and mitral prostheses. She received warfarin daily during her entire postoperative period. At cardiac catheterization shortly before she died, a 4 mm Hg end-diastolic pressure gradient was noted between the right atrium and right ventricle. **a,** view of excised bioprosthesis from the atrial surface showing overgrowth of host tissue over the sewing ring and over the leaflets of the bioprosthesis. All three leaflets were slightly stiffer than normal. **b,** section of one leaflet showing thickening due to host ingrowth and fibrin deposition. **c,** high-power view of area enclosed by the box in **b,** showing fibrin deposits on the leaflet and inflammatory cells **(arrow). d, e** and **f,** high-power views of 1 μ thick sections of the atrial (inflow) surface of the leaflet showing endothelialization (endo.) of the fibrin and red cell thrombus that covers the leaflet. Histiocytes (h) and giant cells (gc) line the leaflet, and the surface of the fibrocollagenous structure is disrupted. (Hematoxylin-eosin stains ×7 **[b],** ×220 **[c];** toluidine blue stain: ×860 **[d, e** and **f],** all reduced by 25 percent.)

therefore appeared to represent endothelialization of thrombus rather than of the porcine tissue. No other late bioprostheses showed endothelialization of the cusps (Fig. 13). Polarization microscopy revealed no foreign bodies in any cusp of any bioprosthesis.

Five of the 18 porcine bioprostheses were in patients who postoperatively were receiving either warfarin sodium (three patients) or aspirin plus dipyridamole (two patients) because they also had mechanical prostheses. In all five bioprostheses in these five patients various degrees of fibrin deposits were evident on the cusps (Fig. 12).

Comments

Previous observations on porcine bioprostheses: Good clinical and usually adequate hemodynamic results have been reported by several groups of investigators in patients who have had porcine heterograft bioprostheses implanted for up to 5 years.[1–9] These studies have shown low rates of clinical episodes suggestive of thromboembolism although long-term anticoagulant agents have rarely been used.[1,4,6,12] Reports of failure of these bioprostheses have been rare.[1,6,9] However, most studies of porcine heterograft prostheses have concerned formalin-fixed tissue or tissue treated with various glutaraldehyde preservation techniques.[3,10,13–19] Few descriptions of structural changes have been reported in valves processed by the Hancock stabilized-glutaraldehyde process, and few bioprostheses prepared by this fixative have been studied late.[10,13]

Examination of formalin-treated porcine bioprostheses showed a high frequency of structural failure. Zuhdi et al.[3] noted structural failure in 20 of 31 stented formalin-fixed porcine bioprostheses within 4 years after implantation. Histologic studies showed inflammatory-cell infiltrates in the cusps, fibrin deposits and histiocyte and giant cell accumulation. However, no degenerative changes were seen in eight glutaraldehyde-preserved bioprostheses in place from 8 days to 16 months.[3]

Carpentier et al.,[6] utilizing a different glutaraldehyde fixation technique and rigid stents, noted valve dysfunction in seven patients with implantation periods of 1 to 5 years. No immunologic reaction was seen, but collagen degeneration with cusp perforation and lining of cusps with histiocytes, macrophages and giant cells was observed.

In 4 of 32 patients with a Hancock glutaraldehyde-fixed bioprosthesis on a semirigid stent in the mitral position, Horowitz et al.[5] noted "normal" histologic features in four valves removed 4 to 29 months after implantation. They also mentioned "moderate numbers of macrophages and a few giant cells" at the base of the muscle shelf of the right coronary cusp in a valve in place for 18 months. Yarbrough et al.[10] noted essentially normal valve structure in six Hancock glutaraldehyde-preserved bioprostheses in place for 14 to 180 days. Mild fibrin deposits and layers of "mesothelial-like cells" were noted in a bioprosthesis in the tricuspid position for 39 days.[10]

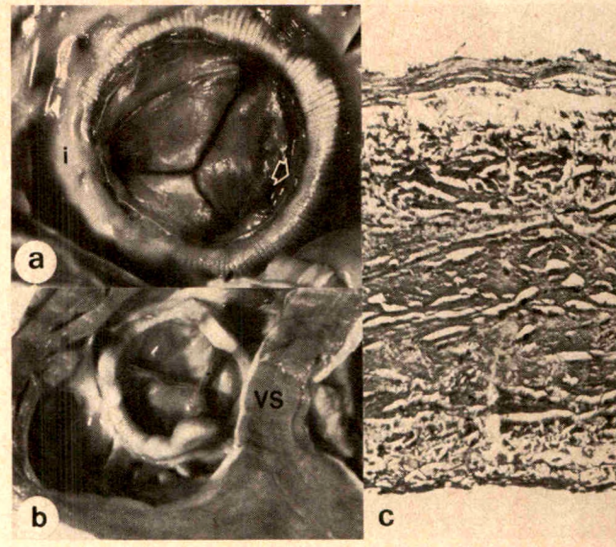


FIGURE 13. Porcine bioprosthesis implanted in the tricuspid valve position 15 months earlier. **a,** view from right atrium. Host connective tissue (i) covers the sewing ring but stops abruptly at the porcine tissue **(arrow). b,** view from right ventricle showing ingrowth of whitish host tissue over struts but not onto the valve leaflets. VS = ventricular septum. **c,** section of one leaflet of the bioprosthesis showing lack of host endothelialization of the leaflet surfaces. (Hematoxylin-eosin stain ×220 **[c]**, reduced by 29 percent.)

Present observations on structural changes: Our study of 51 Hancock bioprostheses (44 examined histologically) showed a high frequency of structural changes, but most of these changes did not affect valve function. Fibrin deposits on the cusp outflow surfaces and inflammatory cells were present in nearly 70 percent of all bioprostheses studied. Almost half of the prostheses showed fibrin deposits on the inflow surfaces. The similar frequency of these changes in both early (implanted for less than 2 months) and late (implanted for more than 2 months) bioprostheses and the lack of organization of the fibrin deposits suggests that fibrin and inflammatory cells begin to be deposited soon after implantation. Perhaps fibrin deposition occurs as a response to structural stresses. However, histiocyte accumulation was slightly less frequent (54 percent) in early than in late (76 percent) bioprostheses, and giant cell formation was more than twice as common in late valves, suggesting that these reactions to the glutaraldehyde-preserved tissue occur later than the fibrin deposits. Although gross leaflet disruption was present in only 3 (17 percent) of 18 late bioprostheses, microscopic-sized focal cusp disruption by host cells was present in 45 percent of the late bioprostheses.

Although the observed histologic changes in the glutaraldehyde-fixed bioprostheses are qualitatively similar to those described in formalin-fixed heterografts, the magnitude of the cell reaction is less. Thus, the Hancock bioprostheses are not biologically inert in man. These findings suggest that the Hancock stabilized-glutaraldehyde preservation technique creates

more stable cross-linking of collagen and less tissue antigenicity than formalin fixation.[3] Collagen degeneration, with valve failure, was noted in the two valves that were in place for the longest periods, thus raising the possibility that cusp fatigue ultimately may occur in many of these bioprostheses. Although clinical studies of the Hancock bioprostheses for up to 5 years are encouraging,[1,9] longer periods of follow-up of patients with such valves will be necessary to ascertain the ultimate fate of the glutaraldehyde-treated valves.

Thromboembolism: implications for anticoagulant therapy: Despite the frequency of gross and microscopic-sized fibrin thrombi, no clear evidence of valve-related thromboemboli was found. Reendothelialization of the valve cusps did not occur, and long-term anticoagulation therapy did not prevent fibrin thrombi. These results suggest that such therapy, at least with warfarin, is not necessary when Hancock bioprostheses are used. Thrombosis with stenosis occurred in 3 of our 41 patients (four bioprostheses). Two of the three had very low cardiac output immediately after operation, and this factor may have contributed to the thrombus formation; the third patient had a 42 mm Hg peak systolic pressure gradient between the left ventricle and a systemic artery, and this gradient may have altered flow in the vicinity of the bioprosthesis and therefore allowed thrombus formation. Horowitz et al.[12] have listed five indications for a 6 week course of anticoagulation after bioprosthetic valve replacement: (1) atrial fibrillation; (2) thrombus in the left atrium at operation; (3) history of thromboembolism; (4) absence of a smooth suture line; and (5) low cardiac output. Our data appear to reinforce at least the last of these indications.

Prosthetic dysfunction: In our study prosthetic dysfunction usually was secondary to technical factors. The struts of a mitral bioprosthesis partially obstructed left ventricular outflow in three patients; all died soon after operation. In only three patients was valve failure the result of degeneration of leaflet tissue.

Of the early bioprostheses studied, the greatest inflammatory reaction seen was in 14 day old tricuspid and mitral bioprostheses from a patient who had removal of an incompetent disrupted mitral bioprosthesis that had been in place for 56 months. This finding suggests that perhaps host sensitization to bioprosthetic antigen was present after destruction of the first bioprosthesis. In the rare patient with bioprosthetic dysfunction, therefore, replacement with a mechanical prosthesis rather than another bioprosthesis may be advisable.

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Pathologic Findings After Cardiac Valve Replacement With Glutaraldehyde-Fixed Porcine Valves

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Although approximately 20,000 glutaraldehyde-fixed porcine cardiac valve prostheses have been implanted in patients there is a lack of detailed pathologic studies of valves removed surgically or examined at necropsy. In this study, of 363 valves implanted in 311 patients, 26 valves (7 percent) from 23 patients (7 percent) were examined morphologically. Of the 23 patients, 14 died intraoperatively or less than 1 month after valve replacement—3 from coronary artery disease, 4 from hemorrhagic myocardial necrosis, 2 from postoperative hemorrhage, 2 from pulmonary disease and 1 from phycomycosis of the prosthesis; in 2 patients no anatomic cause of death was found. Six patients died 1 to 9 months after valve replacement—one from prosthetic thrombotic stenosis, one from prosthetic endocarditis and four from causes unrelated to their prosthesis. Three patients underwent surgical excision of a malfunctioning valve 12 to 31 months after implantation; incompetence was due to infective endocarditis in two patients and to a torn cusp in one.

Fourteen of 15 valves implanted for 1 month or less were normal. Eight of 11 valves implanted for more than 1 month were abnormal: 3 were infected, 2 (from one patient) had focal calcification and thrombosis, 1 had only focal thrombosis, 1 had diffuse thrombosis causing stenosis and 1 had a torn cusp.

In our experience, clinical cardiovascular deterioration in the early postoperative period in patients with glutaraldehyde-fixed porcine valves is unlikely to be related to dysfunction due to pathologic processes affecting the implanted valve. Although postoperative valve dysfunction has been unusual to date, clinical cardiovascular deterioration in the late postoperative period may be related to pathologic processes (infection, thrombosis or degeneration) affecting the implanted valve.

Since 1953 when Hufnagel and Harvey[1] first described successful implantation of a prosthetic device in a patient with cardiac valve disease, numerous prostheses have been used to replace diseased cardiac valves. The complications and pathologic processes associated with the use of such devices vary somewhat depending on the design of the prostheses and the materials used for their construction. There are detailed pathologic studies of patients with caged ball,[2–5] caged disc,[6] tilting disc,[7,8] Hufnagel-trileaflet[9] and various tissue valves.[10–14] However, there is relatively little information concerning the pathologic processes associated with the implantation of glutaraldehyde-fixed porcine heterograft valves (Hancock Laboratories, Anaheim, California) even though an estimated 20,000 of these valves have been implanted.[15] Although several clinical studies have reported pathologic findings in isolated cases,[16–20] only one previous study[21] has focused on pathologic findings associated with the use of this valve.

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TABLE I

Summary of Findings in 20 Necropsy Patients With Porcine Heterograft Valves

Valve Replaced	Sex		Age (yr)		Heart Weight (g)	
	M	F	Range	Mean	Range	Mean
A	8	2	47–83	63	550–960	698
M	3	4	58–72	62	460–680	558
A & M	1	1	35–53	44	600–900	750
M & T	0	1	56		600	
Total	12	8	35–83	60	460–960	653

A = aortic; M = mitral; T = tricuspid.

Patients Studied

Glutaraldehyde-fixed porcine heterograft valves from 23 patients were examined. Fifteen patients had valve replacement at the Peter Bent Brigham Hospital where 312 porcine valves have been implanted in 263 patients from January 1972 to July 1976; 8 patients had valve replacement at the West Roxbury Veterans Administration Hospital where 51 valves have been implanted in 48 patients. Thus, the 23 patients of this study represent 7 percent of all patients who had this type of valve implanted at these institutions. Twenty patients were studied at necropsy; the other 3 had surgical excision of malfunctioning porcine valves. Preoperatively, all 23 patients were in functional class III or IV (New York Heart Association classification[22]). In the group of 20 necropsy patients the age range was 35 to 83 years (mean 60 years); 12 were male (60 percent) and 8 female (Table I).

Valves replaced: Of the 23 native valves replaced in the 20 necropsy patients, 12 (52 percent) were aortic, 10 (44 percent) were mitral and 1 (4 percent) was tricuspid. Of the 12 aortic valves, 3 were purely regurgitant and 9 were primarily stenotic with peak systolic gradients ranging from 14 to 100 mm Hg (mean 57). Aortic regurgitation was caused by rheumatic valve disease in all three cases; aortic stenosis was caused by rheumatic valve disease in two patients, calcific aortic stenosis in two patients and a congenitally malformed valve in five patients (four bicuspid and one unicommissural). Of the 10 mitral valves replaced, 7 were stenotic due to rheumatic disease with a mean diastolic gradient of 8 to 16 mm Hg (mean 12). One of the three regurgitant valves was the result of papillary muscle infarction with ruptured chordae tendineae, one was the result of rheumatic valve disease and the third was associated with an ostium secundum atrial septal defect in a patient who also had tricuspid valve replacement because of regurgitation.

TABLE II

Causes of Death in 20 Patients After Valve Replacement

	Early* Deaths	Late* Deaths	Total
Coronary artery disease	3	0	3
Hemorrhagic myocardial necrosis	4	0	4
Prosthetic thrombotic stenosis	0	1	1
Prosthetic endocarditis	1	1	2
Pulmonary disease	2	0	2
Postoperative hemorrhage	2	0	2
Noncardiac	0	4	4
No anatomic cause	2	0	2
Total	14	6	20

* Early = less than 1 month after implantation; Late = 1 month or more after implantation.

Results

Heart weight: In the 20 necropsy patients heart weight ranged from 460 to 960 g (mean ± standard error of the mean 653 ± 33) (Table I). Hearts from patients with aortic valve disease weighed significantly more (704 ± 43 g) than those from patients with mitral or tricuspid valve disease (564 ± 31 g, $P < 0.05$). There was no significant difference in heart weight of patients who died early rather than late after valve replacement.

Early postoperative deaths: Fourteen patients died less than 1 month after valve replacement: four within 24 hours, six from 1 to 6 days and four from 1 to 4 weeks postoperatively. Although death may have been related to more than one pathologic process, in each patient a single most important cause of death was determined on the basis of pathologic findings (Table II).

Severe coronary arterial atherosclerosis (more than 75 percent luminal narrowing of one or more major coronary arteries) was present in 6 of 14 patients (43 percent) who died early. In three patients who had a recent myocardial infarction, the infarction was considered to be the cause of death (Fig. 1).

Hemorrhagic myocardial necrosis[23,24] in patients without significant coronary artery disease was the cause of death in four patients; all with this lesion had aortic valve replacement and increased left ventricular wall thickness (mean 2.0 cm, normal <1.5 cm).

Postoperative hemorrhage appeared to be responsible for death in two patients. Both patients died within 24 hours of operation.

Prosthetic endocarditis due to phycomycosis caused the early postoperative death of one patient. In this 48 year old man with aortic stenosis the low cardiac output syndrome developed, and he died 13 days postoperatively. Postmortem examination revealed thrombotic material on the stent of the prosthesis with similar thrombi on the aortic intima and within the coronary

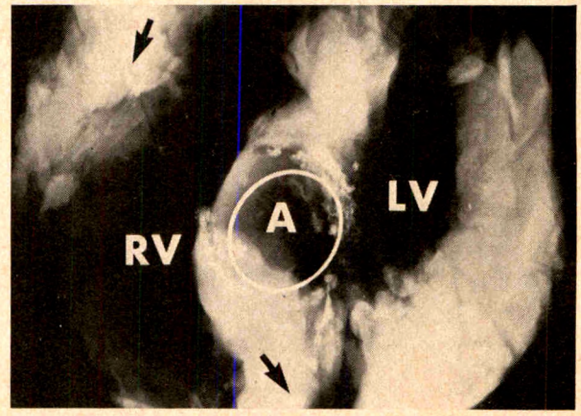


FIGURE 1. Postmortem X-ray film of the heart of a 67 year old man who died of myocardial infarction 16 days after valve replacement for calcific aortic stenosis. In this view from the base toward the apex of the heart, calcifications (**arrows**) within the coronary arteries are evident. There is also heavy calcification of the aortic valve anulus (A). Such calcification could interfere with implantation of the valve, resulting in perivalve leaks. In this patient there was no evidence of prosthetic dysfunction. LV = left ventricular cavity; RV = right ventricular cavity.

arteries (Fig. 2). A left ventricular posterior wall myocardial infarction was also present. Microscopic examination with special stains for fungus revealed organisms with large branching nonseptate hyphae in all thrombi and within the infarcted myocardium (Fig. 2).

Pulmonary disease appeared to be responsible for two deaths. In one patient who died suddenly, multiple pulmonary emboli were found. In the other, a 78 year old woman who died 7 days after emergency mitral valve replacement for severe mitral stenosis, autopsy revealed severe acute and chronic congestion of the lung ("mitral lung") with extensive pulmonary hemorrhage.

No anatomic cause of death was found in two patients. One, a 56 year old woman who died 5 days after mitral and tricuspid valve replacement, had persistent low cardiac output postoperatively. The other, a 64 year old woman, had spontaneous ventricular tachycardia 3 days after operation and could not be resuscitated.

Prosthetic dysfunction due to disproportion, thrombotic stenosis, degeneration or perivalve leak was not found in any patient who died 1 month or less postoperatively. No patients had significant lesions of their remaining native cardiac valves. Microscopically, except for the valve infected with Phycomycetes, all porcine valve leaflets examined appeared intact and normal.

Late postoperative deaths: Six patients died 1 to 9 months after valve replacement (Table II). Two deaths were related to pathologic processes involving the implanted porcine valves. In one patient, an 83 year old man who did very well initially but had congestive heart failure 14 weeks after aortic valve replacement with a no. 23 valve, there was severe prosthetic stenosis (postmortem valve area by planimetry 0.61 cm^2) caused by large thrombi on the aortic surface of all three valve leaflets which narrowed the valve orifice and almost certainly interfered with valve function (Fig. 3). This

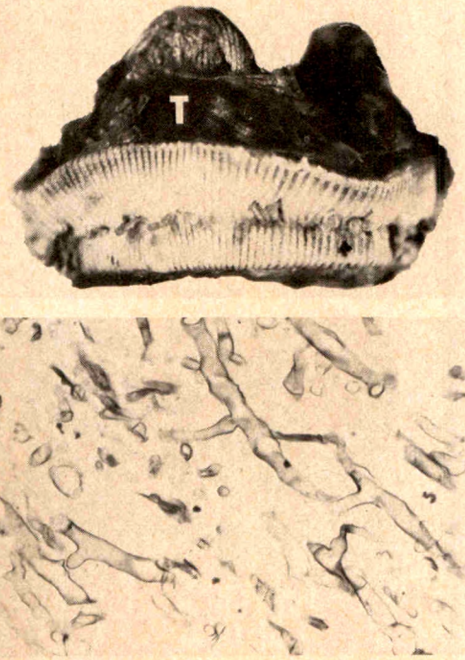


FIGURE 2. Porcine heterograft valve (**top**) from a 48 year old man with aortic stenosis who had low cardiac output postoperatively and died 13 days later. At autopsy thrombosis (T) primarily involving the stent of the prosthesis was present. Thrombus was also present in the aorta and epicardial and intramyocardial coronary arteries. Histologic sections (**bottom**) showed that fungi of the class Phycomycetes were present in all thrombi and within an area of myocardial necrosis. (Methenamine silver stain ×252, reduced by 7 percent.)

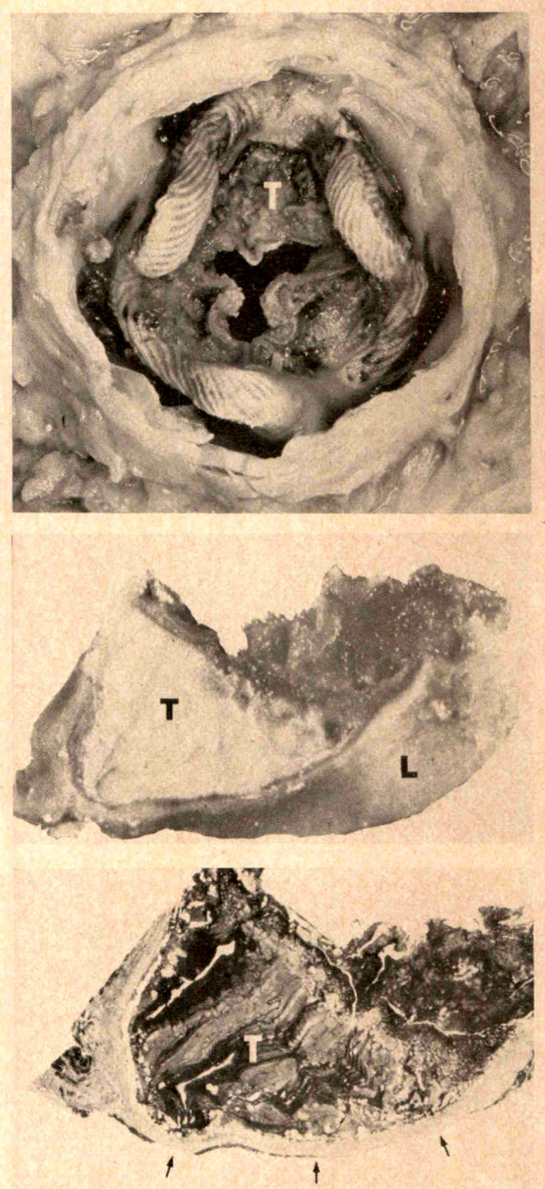


FIGURE 3. Porcine valve from an 83 year old man who had intractable congestive heart failure 14 weeks after aortic valve replacement. Thrombotic prosthetic stenosis (orifice area by planimetry 0.61 cm^2) was the cause of heart failure and death. There is thrombosis (T) of the aortic surfaces of all three leaflets (**top**). Gross sections of the leaflets (L) (**middle**) showed organizing thrombus (T) with more superficial recent thrombus. Histologic sections (**bottom**) showed that the thin valve leaflets (**arrows**) were intact but covered with dense organizing thrombus (T). (Movat pentachrome stain ×9, reduced by 10 percent.)

patient was receiving estrogen therapy for prostatic carcinoma. The other patient, a 58 year old man who had aortic valve replacement, had mediastinitis postoperatively that seemed to resolve with antibiotic therapy. However, 5 weeks after operation and 2 weeks before death, he had pseudomonas septicemia that did not respond to therapy. At necropsy, mediastinitis was present. The infection involved the aorta with erosion of the wall and massive hemorrhage. The porcine valve showed evidence of healed prosthetic endocarditis with a well organized vegetation that was composed primarily of collagenous tissue with no organisms or acute inflammation (Fig. 4).

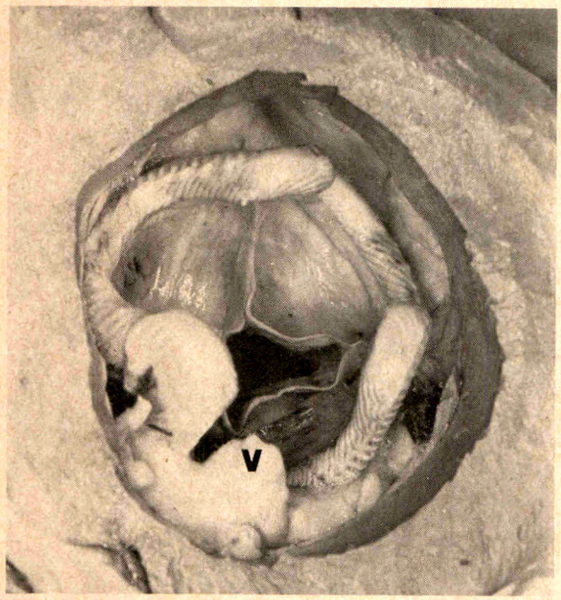


FIGURE 4. Porcine valve in the mitral position in a patient who died from pseudomonas septicemia 7 weeks after valve replacement. Although active infection was found in the mediastinum and aorta the porcine valve leaflets were normal and only a healed vegetation (V) was present on the valve stent. Note that connective tissue ingrowth has occurred over the commissural supports of the stent.

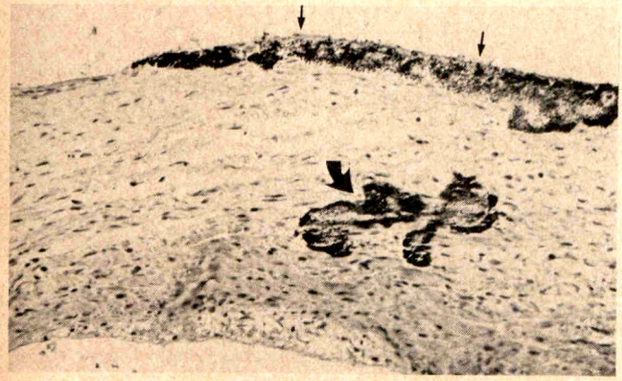


FIGURE 5. Calcification (**arrows**) on surface and within leaflet of a porcine valve in a patient receiving long-term hemodialysis who died of renal failure 6 months after aortic and mitral valve replacement. The calcification caused mild thickening of the valve leaflets. Although not functionally significant in this patient, such calcification could result in loss of pliability of the leaflets and valve dysfunction. (von Kossa stain ×40.)

Two patients who had chronic renal failure died of their renal disease. Both of these patients also had significant coronary artery disease but no acute infarction. One patient with chronic active hepatitis died of his liver disease. Another patient, a 53 year old woman with double valve replacement who had been receiving long-term warfarin therapy for recurrent pulmonary emboli, died of intracerebral hemorrhage. This was the only patient who died late after valve replacement who was receiving long-term anticoagulant therapy.

Status of porcine valves in late deaths: As stated, two patients died as a result of prosthetic-related problems: thrombotic stenosis and infective endocarditis. However, in two of the four patients who died of other causes, there were abnormalities of the prostheses. In one patient who died of renal failure, a 35 year old man with aortic and mitral valve prostheses who had had long-term hemodialysis therapy, both prostheses had focal adherent thrombi on the valve leaflets. In addition, both leaflets had areas of thickening with yellow discoloration that, on microscopic examination, were found to be calcifications within the porcine valve leaflets (Fig. 5). Although the patient had been dialyzed for chronic renal failure, his serum calcium levels had never become elevated, and the only other calcifications found were in myocardial scars in the region of the mi-

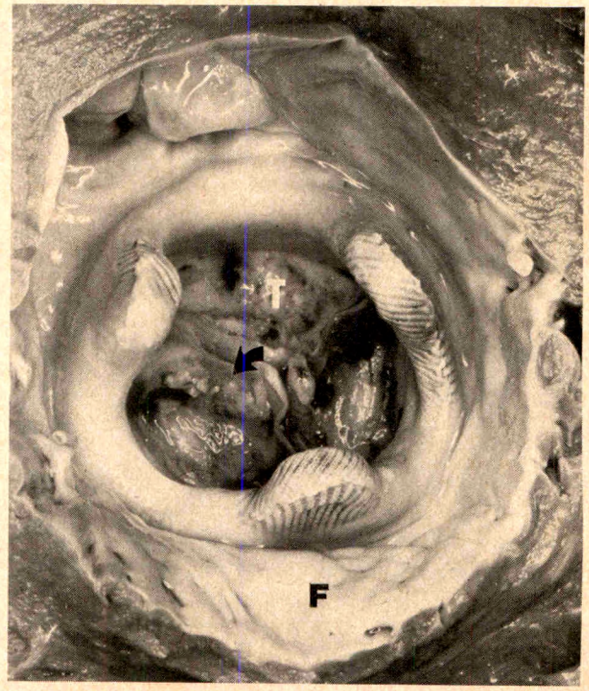


FIGURE 6. Porcine valve in the mitral position in a 60 year old woman who died of renal failure 4 months after valve replacement. At necropsy, there was left ventricular endocardial fibroelastosis (F). Connective tissue ingrowth has covered all but the tips of the stent. Thrombus (T) fills the sinus of one leaflet, and small focal thrombi (**arrow**) are present on another. There was no clinical evidence of prosthetic dysfunction.

TABLE III

Data on Three Patients With a Surgically Removed Porcine Prosthesis

Patient no.	Patient's Age at Removal (yr)	Valve Replaced	Etiology of Valve Disease	Functional Lesion	Cause of Prosthetic Failure	Duration of Implantation
1	79	Aortic	Rheumatic	Aortic regurgitation	Streptococcus viridans endocarditis	31 mo
2	28	Mitral	Bacterial endocarditis	Mitral regurgitation	Candida paropsilosis endocarditis	12 mo
3	44	Mitral	Rheumatic	Mitral regurgitation	Torn leaflet	31 mo

tral valve anulus. Another patient with chronic renal failure had focal thrombosis but no calcification of the valve prosthesis (Fig. 6).

Surgically excised valves: Three patients required removal of malfunctioning porcine valves (Table III). In two patients whose valve prosthesis was removed 31 months and 12 months, respectively, after implantation, infective endocarditis (Streptococcus viridans and Candida paropsilosis) caused sepsis and valve incompetence (Fig. 7). The patient with candida endocarditis had required valve replacement because of infective endocarditis related to abuse of injectible narcotic drugs. The fungal prosthetic endocarditis may have been related to resumption of such injections. A third patient, a 44 year old woman, had congestive heart failure and a systolic murmur 31 months after valve replacement. At reoperation one cusp of the porcine prosthesis was torn (Fig. 8); pathologic examination revealed no infection or inflammation of the torn cusp.

Thus, of 11 valves implanted for 1 to 31 months, 3 were infected: one by Candida paropsilosis, one by Streptococcus viridans and one by Pseudomonas aeroginosa. Of the eight noninfected valves, 5 were abnormal, 2 had focal thrombosis with calcifications, 1 had only focal thrombosis, 1 had diffuse thrombosis causing prosthetic stenosis and, in the only valve with primary structural failure, a cusp was torn from the strut of the flexible stent (Table IV).

Comments

Although many types of prostheses have been used to replace malfunctioning cardiac valves, an ideal substitute has yet to be found. The glutaraldehyde-fixed porcine valve has several advantages over valves composed entirely of synthetic materials: (1) It has central flow characteristics providing adequate hemodynamic performance, and (2) it appears to be less thrombogenic without long-term anticoagulation in most pa-

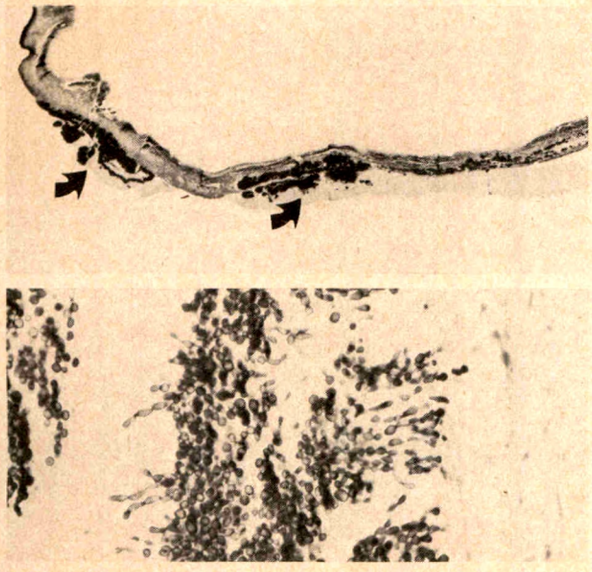


FIGURE 7. Low power (×25) photomicrograph (**top**) of a leaflet of a porcine valve from a 28 year old man who abused injectable drugs and had prosthetic endocarditis and valve incompetence 12 months after valve replacement. Note that colonies of fungi (**arrows**) are invading the valve leaflet. High power (×252) (**bottom**) examination showed the dimorphic growth pattern typical of candida species. Further studies showed that the infecting organism was Candida parapsilosis, the candida most often causing endocarditis in drug addicts (methenamine silver stain).

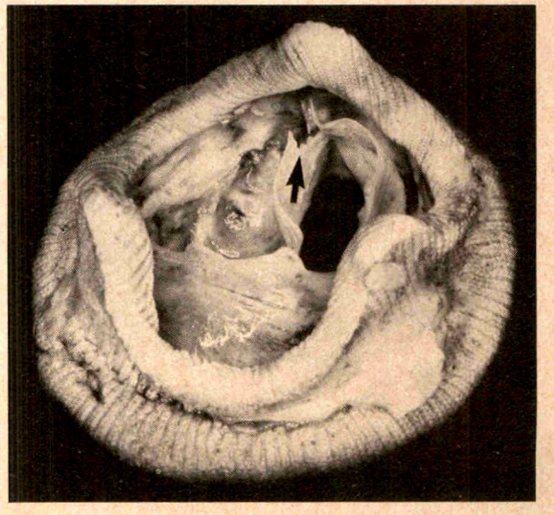


FIGURE 8. Porcine valve from a 44 year old woman who had congestive heart failure and a systolic murmur 31 months after mitral valve replacement. Note the tear (**arrow**) responsible for valve incompetence. There was no evidence of infection or inflammation of the torn leaflet.

TABLE IV

Status of 11 Porcine Heterograft Prostheses Implanted For More Than 1 Month

	Aortic	Mitral	Total
Infection			
Fungal	0	1	1
Bacterial	1	1	2
Focal thrombosis	0	1	1
Focal thrombosis and calcification	1	1	2
Diffuse thrombosis	0	1	1
Torn cusp	0	1	1
Normal	2	1	3

tients.[15,20,25–27] In addition, this prosthesis has an important advantage over other tissue valves in that it appears to be more durable than formalin-fixed porcine valves or valves composed of other human or mammalian tissues.[10]

Early valve changes: Our study indicates that pathologic changes in implanted porcine valves are uncommon in the early postoperative period (1 of 15 valves) but more common (8 of 11 valves) in the late postoperative period. Of 15 valves implanted for less than 1 month, 14 were entirely normal. The only abnormal valve was infected with Phycomycetes, an opportunistic fungal organism that almost certainly was an environmental contaminant at the time the patient underwent valve replacement. Prosthetic disproportion, which according to autopsy studies may be an important cause of early death in patients with caged ball,[3] caged disc[6] or even tilting disc prostheses,[7] has been documented only rarely with a porcine heterograft valve[21] and was not observed in any of our patients. Degeneration would not be expected to be a problem with the porcine valve in the early postoperative period (and was not) and, although thromboembolism is a possible problem, prosthetic thrombosis was not observed in any valve implanted for 1 month or less.

Late valve changes: In the late postoperative period, 8 of 11 valves implanted for 1 to 31 months were abnormal; 3 were infected. Postoperative prosthetic endocarditis is a significant problem with porcine valves as with other cardiac valve prostheses[7,28,29];however, antibiotic therapy may be more effective in treating infections of porcine tissue valves. In one patient, although active pseudomonas infection persisted in other organs, healing of an infected valve occurred without the need for reoperation (Fig. 4). We have also documented an antibiotic "cure" of staphylococcal endocarditis in a patient 6 months after mitral valve replacement with a porcine valve,[27] and Magilligan et al.[30] have documented seven of nine antibiotic "cures" of late postoperative endocarditis of porcine heterografts.

One important advantage of the glutaraldehyde-fixed porcine valve is that anticoagulation therapy is usually not needed because thromboembolic complications are unusual. Anticoagulation, however, is indicated in most patients with mitral bioprostheses who have chronic atrial fibrillation.[17,27,31] In our study thromboses occurred on four of eight noninfected valves examined late postoperatively. The patient with the thrombotic prosthetic stenosis, an 83 year old man with prostatic carcinoma, was receiving estrogen therapy, which may increase blood coagulability.[32,33] The three valves with focal thrombosis were from two patients receiving hemodialysis for renal failure. Two valves from one of these patients also had foci of calcification within the porcine valve leaflets. Patients with renal failure who are receiving hemodialysis have complex metabolic abnormalities and may be more susceptible to thrombosis and calcification of implanted valves, as well as chronic bacteremia and infection. Because tissue valves are not biologically inert,[21] perhaps they should be used with caution in patients in whom infiltrative processes, such as calcification, are likely to occur.

Collagen degeneration, a well known complication of other tissue valves,[10–14] occurred in only one valve in our series. This was in a woman who had a 19 mm Björk-Shiley aortic valve prosthesis and a porcine mitral valve bioprosthesis implanted for 31 months. Additional follow-up studies are needed to establish the magnitude of this problem in patients with glutaraldehyde-fixed porcine valves.

In conclusion, clinical deterioration in the early postoperative period in patients who have undergone cardiac valve replacement with porcine valves is unlikely to be related to valve dysfunction. Although to date late postoperative valve dysfunction has been uncommon, clinical cardiovascular deterioration in the late postoperative period may be related to pathologic processes (thrombosis, infection or tissue degeneration) affecting the implanted valve.

Acknowledgment

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Clinical Experience With the Smeloff-Cutter Aortic Valve Prosthesis: An 8-Year Follow-Up Study

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A total of 46 patients who survived aortic valve replacement with the present model Smeloff-Cutter prosthesis between 1968 and 1973 were followed up postoperatively. All patients received oral anticoagulant therapy. The average age at implantation was 44 ± 13 (mean ± standard deviation) years; 36 patients were male and 10 were female. The valve damage was caused by rheumatic disease in 19 (41 percent), infective endocarditis in 14 (30 percent), congenital heart disease in 7 (15 percent) and other factors in 6 (13 percent). Late death occurred in eight patients (17 percent). All available patients were followed up until December 1976. During the 8 years of follow-up study, seven patients, including four heroin addicts, had postoperative endocarditis (15 percent); five of the seven had cerebral involvement, possibly from septic emboli. Four patients were reoperated on; three had active endocarditis and one had a high transvalve pressure gradient. The mean follow-up time was 4.9 years per patient. Of the 38 living patients, 33 have functional improvement and are still being followed up. Only one patient had a bland embolism to a systemic artery. No ball variance or other types of material failure have been detected. Although the chronic aspects of valve disease remain after prosthetic valve replacement, the Smeloff-Cutter aortic prosthesis deserves strong consideration when selecting a rigid prosthesis for aortic valve replacement.

The current model Smeloff-Cutter aortic valve prosthesis has been in use since September 1966 without further modification in either material or design.[1] Nevertheless, the literature available on its use is scanty when compared with that available for Starr-Edwards valve prostheses. Previous reports[1–3] on the experience with the current model Smeloff-Cutter prosthesis are encouraging because of the low incidence rate of thromboembolism and the absence of material failures. However, some reports[4,5] have included both the Smeloff-Cartwright-Davey-Kaufman (SCDK) and Smeloff-Cutter valve types and have not clarified the extent to which each valve type contributed to the complications and long-term results.

The Smeloff-Cutter prosthesis was used in 46 patients for aortic valve replacement between 1968 and 1973 at our Medical Center. This report reviews our follow-up of these patients through December 1976.

Patients Studied

The subjects studied were 46 patients who had Smeloff-Cutter aortic valve replacement at the Los Angeles County-University of Southern California Medical Center between 1968 and 1973. Thirty-eight patients are still alive. Thirty-three are still being followed up in our outpatient department, and five by private physicians.

A descriptive analysis of the patients, whose average age is 44 ± 13 years (mean ± standard deviation) (range 25 to 72), is given in Table I. The anatomic diag-

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TABLE I

Data on 46 Patients With a Smeloff-Cutter Aortic Prosthesis (1968–1972)

	no.	%
Sex		
Male	36	78
Female	10	22
Ethnic group		
Spanish surname	8	18
White	19	41
Black	18	39
Chinese	1	2
Anatomic diagnosis		
Regurgitation	23	50
Stenosis	14	30
Combination	9	20
Etiology		
Rheumatic heart disease	19	41
Infective endocarditis	14	31
Congenital heart disease	7	15
Other	6	13
Usual rhythm		
Normal sinus rhythm	44	96
Paced	2	4

TABLE II

Long-Term Survival of 46 Patients With an Aortic Smeloff-Cutter Prosthesis Followed Up Between 1968 and 1977

Year of Entry (Implantation)	Now Followed Up in Clinic	Followed Up Elsewhere	Deaths	Total
1968	2	0	1	3
1969	6	0	2	8
1970	3	1	1	5
1971	14	1	1	16
1972	8	3	3	14
Total	33 (72%)	5 (11%)	8 (17%)	46 (100%)

nosis indicates the predominant valve lesion at the time of surgery. The etiology of these lesions was established after reviewing the clinical summary, cardiac catheterization results and operative notes. The 14 patients grouped under infective endocarditis included 8 patients with a history of drug addiction. Two patients received aortocoronary bypass grafts in addition to valve replacement. At the time of operation two patients were in New York Heart Association functional class[6] I, two in class II, 26 in class III and 16 in class IV. Patients in classes I and II were operated on because of frequent syncopal episodes. Of 16 patients in class IV, 8 had severe aortic regurgitation due to infective endocarditis; all 8 used heroin intravenously.

Table II shows the number of patients entering the study each year and the number surviving. Table III analyzes the patient group according to size of prosthesis; the majority of patients received small prostheses, that is, sizes A1, A2 or A3.

Warfarin was administered to all patients in an attempt to maintain prothrombin level between 10 and 20 percent of control level throughout the study period. Neither aspirin nor dipyridamole was prescribed. Three patients had postoperative cardiac catheterization. Fifteen patients had phonocardiography and measurement of systolic time intervals. Sixteen patients had measurement of serum haptoglobin and lactic dehydrogenase levels and examination of urine for hemosiderin in addition to the regular hemoglobin and hematocrit estimations.

Results

Mortality: During the 8-year follow-up period there were eight deaths (17 percent) (Table IV); four patients died of endocarditis, one of myocardial infarction, one of lung cancer, one of severe gram-negative sepsis and empyema and one of sudden unexplained cause.

Endocarditis: Seven patients required treatment for postoperative endocarditis. Four of seven were heroin

TABLE III

Valve Size Distribution in 46 Patients

	Size of Smeloff-Cutter Valve						
	A1	A2	A3	A4	A5	A6	A7
Primary flow orifice (cm^2)	1.19	1.54	1.83	2.05	2.31	2.85	3.45
Patients (no.)	8	10	17	7	2	1	1

TABLE IV

Late Mortality

Case no.	Age at Death (yr)	Etiology of Valve Disease	Cause of Death	Months Postoperative*
1	44	RHD, AS	Gram-negative sepsis, empyema	1.7
2	48	IE, AI	Ventricular arrhythmia	2.4
3	37	RHD, IE, AI	Cerebral hemorrhage secondary to endocarditis	37.6
4†	39	IE, AI	Candida endocarditis	43.8
5†	35	CHD, AS	Candida and staphylococcus endocarditis, cerebral infarction	80.6
6	50	IE	Staphylococcus endocarditis, gastrointestinal bleeding	37
7	46	RHD	Possible ventricular arrhythmia	48
8	66	ASH, AI	Cancer of lung, metastatic	96

* After initial valve replacement.

† These patients had a Bjork-Shiley aortic valve prosthesis at the time of death. Smeloff-Cutter valves were removed because of Candida sepsis.

AI = aortic insufficiency; AS = aortic stenosis; ASHD = arteriosclerotic heart disease; CHD = congenital heart disease; IE = infective endocarditis; RHD = rheumatic heart disease.

TABLE V

Postoperative Endocarditis

Case no.	Etiology	Preoperative Endocarditis (Date)	Date of 1st Valve Replacement	Postoperative Endocarditis (Date)	Treatment	Date of 2nd Valve Replacement	Outcome
4	IE	Candida krusei (April '71)	5-10-71	Candida paropsilosis (8-25-72)	5 FC, amphotericin, miconozole	9-25-73 (B-S)	Death due to endocarditis 12-19-74
6	IE	Candida (July '72)	8-21-72	Enterococcus (July '73)	Penicillin, streptomycin	8-13-73 (S-C)	Death due to endocarditis 10-24-74
9	IE	Streptococcus, group D (July '72)	8-14-72	Candida paropsilosis (5-12-74)	5 FC, amphotericin	5-5-75 (porcine).	Alive
5	CHD	None	4-28-69	Candida paropsilosis grew from vegetation removed at 2nd valve replacement	Amphotericin	5-29-75 (B-S)	Death due to endocarditis 12-16-75
3	RHD; IE	Streptococcus (1960)	5-23-69	Actinobacillus (5-12-72)	Penicillin	None	Death due to endocarditis 6-27-72
10	RHD	None	9-11-70	Streptococcus, mixed (6-28-72)	Penicillin, streptomycin	None	Alive. Free of endocarditis
11	RHD	None	11-20-69	Staphylococcus aureus	Methicillin	None	Alive. Free of endocarditis

B-S = Bjork-Shiley; CHD = congenital heart disease; 5 FC = 5 flucytosine; IE = infective endocarditis; RHD = rheumatic heart disease; S-C = Smeloff-Cutter.

addicts and had had endocarditis before the valve replacement. Table V summarizes the details of pre- and postoperative endocarditis including cause, date of onset, date of valve replacement and outcome.

Thromboembolism: Two patients had pulmonary embolism on one occasion; both recovered uneventfully. A 56 year old man had mild transient expressive aphasia 6 years after valve replacement. He represented the only case of bland systemic embolism detected in our patient group.

Anticoagulation-related problems: Four patients required hospitalization for anticoagulation-related problems, including hematuria (one occasion), bleeding into the knee (one occasion), a large hematoma secondary to an intramuscular injection (one occasion) and poor control of anticoagulation (three occasions).

Hemolysis: Fifteen of 16 patients had mild hemolysis as evidenced by increased serum lactic dehydrogenase or decreased haptoglobin or presence of urinary hemosiderin. Of those with hemolysis, only one woman was found to be anemic; she also had severe menometrorrhagia. Her anemia resolved after a hysterectomy.

TABLE VI

Systolic Time Interval Data on 15 Patients With Size A1 to A3 Smeloff-Cutter Prosthesis

Interval or Index	Range (msec)	Mean ± SD (msec)	Normal range (msec)
LVETC	366–466	481 ± 33	395 ± 13
Ascending index	0.41–0.86	0.66 ± 0.15	0.20 – 0.36
Upstroke time*	109–277	207 ± 58	>150

*13 of the 15 patients had an upstroke time of more than 150 msec.

LVETC = left ventricular ejection time corrected for heart rate; SD = standard deviation.

Although not studied preoperatively, 6 of 16 patients who were part of a previous study[7] were found to have gallstones when oral cholecystography was performed 18 months or longer after valve replacement. In this small group, 5 of 11 men (45 percent) and 1 of 5 women (20 percent) had gallstones.

Phonocardiography: Phonocardiograms were obtained 1 to 69 months (mean 18) postoperatively from 15 patients with A1, A2 and A3 Smeloff-Cutter aortic valves. All 15 patients were in New York Heart Association class I and none had had a thromboembolic episode. The ratio of opening to closing click was recorded at the frequency range 100 to 300 hertz in the second right intercostal space. A ratio of less than 0.7 has been considered suggestive of ball variance and, in one report,[8] a ratio of less than 0.5 an indication for valve replacement. The latter report evidently pertained to valves produced before September 1966 because no case of ball variance has been documented in Smeloff-Cutter valves produced after that date.[1] In our 15 patients the ratio of opening to closing click was found to be 0.34 to 2.3 (mean ± standard deviation 0.9 ± 0.4). Three patients had a ratio of less than 0.5 with no evidence of valve dysfunction, indicating that this ratio may not be a reliable indicator for Smeloff-Cutter valve replacement.[9]

Systolic time intervals: The 15 patients who had phonocardiograms also had measurements of systolic time intervals from recordings made at the second right intercostal space. The intervals measured were left ventricular ejection time corrected for heart rate, upstroke time and ascending index (Table VI). The majority of systolic time intervals suggested left ventricular outflow obstruction.

Catheterization: Three patients had transseptal cardiac catheterization 2 to 6 years after valve implan-

TABLE VII

Results of Cardiac Catheterization in Three Patients with Size A1 Smeloff-Cutter Prosthesis

Case no.	Preoperative Data: Mean Aortic Valve Gradient (mm Hg)	Preoperative Data: CO	Preoperative Data: CI	Postoperative Data: Months Postop	Postoperative Data: Mean Prosthetic Valve Gradient (mm Hg)	Postoperative Data: CO	Postoperative Data: CI
12	44	. . .	. . .	42	25	3.32	1.74
5	45 R	4.49	2.74	71	30	7.30	3.87
	70 E	8.07	4.92				
13	60	6.10	2.90	24	50	5.41	2.79

CI = cardiac index (liters/min per m^2); CO = cardiac output (liters/min); E = exercise; R = rest.

TABLE VIII

Improvement in Functional Class of 46 Patients With a Smeloff-Cutter Aortic Prosthesis (Follow-Up Period January 1968 to January 1977)

New York Heart Association Functional Class: Before Valve Replacement		After Valve Replacement: I	II	III	IV	Followed Up Elsewhere	Deceased	Total
I	2 (4%)	1	1	0	0	0	0	2
II	2 (4%)	1	1	0	0	0	0	2
III	26 (57%)	6	14	1	0	2	3	26
IV	16 (35%)	3	4	1	0	3	5	16
Total		(24%)	20 (44%)	2 (4%)	0 (0%)	5 (11%)	8 (17%)	46 (100%)

tation to determine transvalve pressure gradient (Table VII). All three patients had size A1 valves (primary flow orifice 1.19 cm^2) and had a moderate to large mean transvalve pressure gradient at rest.

Reoperation: Four patients required prosthetic valve replacement—two in an attempt to eradicate chronic Candida endocarditis, one to correct a severe paraprosthetic leak associated with group D streptococcus and one in an attempt to relieve symptoms considered secondary to a 50 mm peak systolic transvalve gradient. Although all patients survived reoperation, three patients died 7 to 15 months after the second valve implantation.

Improvement in functional status: Thirty-three of the 46 patients are still being followed up in the valve clinic (Table II). Their functional class before and 4 to 8 years after operation is shown in Table VIII. None is in functional class IV, and almost all have shown siginificant improvement in functional class although most received a small prosthesis.

Examination of recovered valves: A total of 21 Smeloff-Cutter aortic prostheses were recovered, 17 at autopsy and 4 at operation. Eighteen were from patients not included in this study because they died in the early postoperative period or had more than one valve replaced by a prosthesis. Eight of the 21 valves were recovered 12 to 73 months after implantation. One aortic valve recovered from a patient who had undergone aortic and mitral valve replacement 12 months earlier showed minimal thrombus on one upstream and one downstream strut. Another aortic valve was recovered 13 months after the patient had undergone aortic, mitral and tricuspid valve replacement; it showed minimal thrombus on one downstream strut. The other 19 recovered valves were thrombus-free. No evidence of ball variance was seen in any of the recovered valves.

Discussion

Design features of Smeloff-Cutter prosthetic valve: The search for the ideal prosthetic valve continues.[10] Most commercially available valve prostheses have been subject to changes in design and material. In this respect the Smeloff-Cutter valve prosthesis is unique; it has been in clinical use for more than a decade without change in design or material. The forerunner of the Smeloff-Cutter prosthesis, the SCDK prosthesis, was conceived in 1961,[11] used clinically in the latter part of 1963 and put into commercial production on October 1, 1964. The first model of the Smeloff-Cutter prosthesis became available in early 1965 and was used clinically until September 1966 when the second (present) model became available commercially. This model utilizes a mild cure process for the silicone rubber occluder, which is selected for orifice clearance at body temperature for each individual prosthesis. These steps have apparently eliminated the problem of ball variance,[12] which has not been observed in the present model since its production in September 1966.

The SCDK and the Smeloff-Cutter prostheses all shared certain design features that are distinctive compared with conventional prostheses of the caged ball type. These features include one piece titanium construction without welds, the use of a double cage and the incorporation of the full flow orifice principle.[13] Both the cages employed are of open construction; that is, the partial struts do not meet to form an apex. The full or-

ifice principle utilizes a spherical occluder that seats at its equator in the closed position and is smaller than the orifice diameter by 0.08 to 0.13 mm. This design feature results in a smaller less massive occluder and a shorter cage on the distal side of blood flow than those of a comparable ball valve of the conventional type. The Smeloff-Cutter prosthesis is advantageous in cases requiring a small valve.

Mortality: Clinical experience with the Smeloff-Cutter aortic valve appears favorable in many respects. Lee et al.[2] recently reported data on 153 operative survivors after single aortic valve replacement with the Smeloff-Cutter prosthesis. Their data show a 22 percent late mortality rate for patients followed up from 1 to 8 years. Smeloff[14] reported a 17 percent late mortality rate in his group of 82 operative survivors followed up for 6 1/2 years. More recently, McHenry et al.[1] reported on a combined group of 229 patients with single aortic and single mitral valve replacement using the Smeloff-Cutter prosthesis; late mortality in this group was 20 percent for a follow-up period of 1 to 8 years. Our data show a 17 percent late mortality rate (8 deaths in 46 patients followed up from 1 to 8 years) (Table IV).* The 5 year survival data for recipients of Starr-Edwards aortic prosthetic models 2310, 2320, 1200 and 1260 who were receiving anticoagulant therapy were reported by Bonchek and Starr[15]; there was a 19 ± 3.7 percent (mean ± 1 standard error) mortality rate for the models 1200 and 1260, and a 19 ± 4 percent mortality for models 2310 and 2320. Although our patient group is small, the mortality rate was lower than that of other reports.

Lee et al.[2] compared their actuarial survival data for 8 years of follow-up experience with aortic valve replacement using the Smeloff-Cutter prosthesis with similar data for the Starr-Edwards prosthesis from the Mayo Clinic. The actuarial curves are virtually identical but are somewhat below the curve of Bonchek and Starr[15] for models 1200 and 1260 Starr-Edwards aortic valves.

Endocarditis after valve replacement: Kloster[16] stated that the incidence rate of postoperative endocarditis is close to 4 percent, but varies from less than 1 to more than 10 percent. His review suggested that endocarditis occurring late after valve replacement responded better to treatment and was associated with lower mortality rates than were cases of early onset. In our series there was a 15 percent incidence rate (7 of 46 patients) of late (1.8 to 53 months) prosthetic valve endocarditis (Table V); 4 of the 7 were heroin addicts and they continued drug abuse after valve replacement. Endocarditis resulted in death in four of seven patients (57 percent mortality rate). One of the three patients with no history of drug abuse died compared with three of the four patients with such a history.

Valve replacement may be life-saving when patients have severe valve destruction due to infective endocarditis. However, if patients continue abuse of intravenously administered drugs, endocarditis is likely to recur. If the organism cultured is the same as the one isolated from blood before valve replacement, the possibility of persistent endocarditis arises. In our four patients who had endocarditis before valve replacement the organisms involved before and after operation were different (Table V).

Systemic thromboembolism: Smeloff[14] reported a 3.6 percent incidence rate of thromboembolism in 100 anticoagulant-treated patients with a Smeloff-Cutter aortic prosthesis over 6 1/2 years. However, in a larger group of 229 patients followed up for 8 years, including both patients with single aortic or single mitral valve replacement, the incidence of thromboembolism was 6 percent.[1] Lee et al.[2] reported a 15 percent incidence rate of thromboembolism in 153 operative survivors with a Smeloff-Cutter aortic prosthesis (24 patients) during a 1 to 8 year follow-up period. However, 7 of the 24 patients who had embolism were not receiving anticoagulant therapy, and in 2 patients the status of anticoagulation was not known. Four of the six patients who had fatal embolic events were not receiving anticoagulant agents. In a 5 year study by Bonchek and Starr[15] there were no thromboembolic events in 116 patients with Starr-Edwards models 2310 or 2320 aortic prostheses. However, in 134 patients who were not receiving anticoagulant therapy, there were 8.8 emboli/100 patient years (average follow-up period 1.7 years). In our study there was only one episode of bland systemic embolism during an average follow-up period of 4.9 years (range 1 to 8 years). Lack of thrombus formation on 19 of 21 Smeloff-Cutter valves recovered at autopsy or surgery also supports our data. The small incidence of bland systemic thromboembolism in our group may be related to the adequacy of anticoagulant therapy or the special design features of the valve prosthesis, or both.

Hemolysis and gallstones: An increased incidence of gallstones after valve replacement was first described by Merendino and Manhas.[17] The association was attributed to incipient hemolysis produced by valve prostheses. Although mechanical hemolysis was not sufficient to cause anemia in our patients, there was an increase in the incidence of gallstones.

Hemodynamic performance of the Smeloff-Cutter prosthesis: Available clinical data are limited, as is true for most commercially available valves. Transvalve pressure gradients depend on the cardiac output and the shape of the blood flow curve, size of the prosthetic valve primary flow orifice in relation to ventricular pressure, size of the aortic root and its relation to the base of the prosthesis, heart rate and peripheral vascular resistance, and many of these factors are not specified in published clinical studies. Thus it often is difficult to compare the results of different investigators.

McHenry et al.[1] reported that the average transvalve pressure gradient in 26 patients with aortic valve replacement by the Smeloff-Cutter prosthesis was 18.4 mm Hg for an average flow rate of 5.4 liters/min, rising

* However, two patients had an infected Smeloff-Cutter valve replaced with a Bjork-Shiley valve 7 and 15 months, respectively, before death. With exclusion of these patients, the mortality rate would be 14 percent (6 of 44 patients).

to an average gradient of 28.4 mm Hg with exercise at an average flow rate of 7.8 liters/min. These resting values, if it is assumed that the average primary orifice area in their 26 patients was of the order of 2 cm^2, are consonant with an acceptable criterion offered by Sauvage et al.[18] According to the latter, the ideal aortic valve prosthesis should have no more than a 20 mm Hg mean systolic pressure decrease for pulsatile flow rates of 2.5 liters/min per cm^2 of valve orifice area. Much lower pressure gradient values were reported by Lee et al.,[19] who measured an average peak systolic gradient of 3.9 ± 10 mm Hg (standard error of the mean) in eight patients after operation. However, the significance of the ± 10 mm Hg is not clear, because it implies the possibility of a negative pressure gradient.

It is of interest to compare clinical pressure gradient data with corresponding in vitro data obtained in pulse duplicators. Such comparisons are difficult and often impossible when certain critical data are lacking or not given. We measured the average systolic pressure gradient after operation in three patients with the smallest size Smeloff-Cutter aortic prosthesis (Tables III and VII). It is encouraging that our three data points fall well below the in vitro results for the size A1 Smeloff-Cutter valve given by Sauvage et al.[18]

Bjork and Olin[20] studied the performance of five different prostheses of comparable tissue diameters during identical flow conditions in pulse duplicator systems. At a pulse rate of 70/min, a stroke volume of 70 cc and an aortic pressure of 125/75 mm Hg, a size 4A Smeloff-Cutter valve had a mean systolic pressure drop of 3.8 mm Hg; a size 23 Bjork-Shiley valve had a 2.5 mm Hg pressure drop and a size 9A Starr-Edwards valve had an 11.2 mm Hg pressure drop. The closing delay of the Smeloff-Cutter poppet was identical to that of the Bjork-Shiley valve and the total regurgitation was less than that of the Bjork-Shiley valve.

Messmer et al.[21] tested five prostheses with similar orifice diameters under identical in vitro conditions, that is, 4.5 liters/min of mean flow and 15 liters/min of peak flow. Their results showed that the Starr-Edwards, Smeloff-Cutter, Wada-Cutter and Bjork-Shiley disc valve all had a 10 mm Hg pressure gradient. In a more specific test, Messmer et al. compared the performance of a size 19 Bjork-Shiley valve and a size A1 Smeloff-Cutter valve (19 mm tissue diameters). At a mean flow rate of 4 liters/min (peak flow of 13 liters/min) the pressure gradients were 47 and 55 mm Hg for the Bjork-Shiley and Smeloff-Cutter valves, respectively. Note, however, that the Smeloff-Cutter size A1 valve has a smaller orifice area than does the Bjork-Shiley size 19 valve. In a second test comparing the size 23 Bjork-Shiley and the size A4 Smeloff-Cutter valves (25 and 25.5 mm tissue diameters, respectively) at a mean flow rate of 4.5 liters/min and a peak flow of 17 liters/min, the systolic pressure gradients were 12 and 18 mm Hg, respectively. From these experimental data it appears that the in vitro performance of the Smeloff-Cutter valve is close to that of a tilting disc valve such as the Bjork-Shiley prosthesis. However, in our experience the smaller Smeloff-Cutter aortic prostheses (A1 to A3) produced considerable pressure drop across the valve and a significant prolongation of left ventricular ejection.

Conclusions: We followed up 46 patients with single aortic valve replacement using the present model Smeloff-Cutter valve between 1968 and 1976. There were seven deaths. There was no ball variance, and only one case of thromboembolism was noted. Almost all of the patients showed significant improvement in functional status although most received a small Smeloff-Cutter prosthesis. The hemodynamics of this prosthesis are acceptable and comparable with those of others available commercially. The present model prosthesis has been in use for more than 10 years without problems relating to durability, and long-term patient studies have been favorable. Although the long-term aspects of valve disease remain after prosthetic replacement, we conclude that the Smeloff-Cutter prosthesis deserves strong consideration when choosing a prosthesis for aortic valve replacement.

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Thirteen Year Experience With Aortic Valve Replacement

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Two hundred forty-one patients (163 male, 78 female) underwent isolated aortic valve replacement at the Medical College of Georgia from 1963 to 1976. The mean age was 46 years (range 12 to 72). Thirty-seven percent had aortic stenosis, 39 percent aortic regurgitation and 24 percent mixed valve lesions. One hundred ninety-eight were in New York Heart Association functional class III or IV. Forty-three were in functional class I or II and underwent surgery for endocarditis, severe regurgitation with rapidly increasing heart size or appearance of angina or electrocardiographic signs of ischemia.

The long-term clinical characteristics of five models of Starr-Edwards valves (1000, 1200, 2300, 2310 and 2320) and the Björk-Shiley prosthesis were defined by rates of survival, complications and rehabilitation. In 212 patients who survived operation, the annual valve-related cardiac mortality rate calculated by the life table method was 4.8 percent for those with model 1000, 3.6 percent for those with model 1200, 7.1 percent for those with model 2300, 6.1 percent for those with model 2310, 3.7 percent for those with model 2320 and 4.0 percent for those with the Björk-Shiley prosthesis. Complications were most frequent among patients with models 2300 and 2310. The model 2320 valves have posed the greatest embolism risk (7.1 episodes/100 patient years compared with 3.3/100 for the entire group). One hundred twelve current survivors (90 percent) are in functional class I or II. No patient in class IV preoperatively survived the full study period. Thirty-nine percent of those in class III and 91 percent of those in classes I and II preoperatively survived 13 years.

Successful management of patients with an aortic valve prosthesis is based upon knowledge of the natural history of individual prostheses. Longevity and rehabilitation depend upon aortic valve replacement before severe myocardial decompensation occurs plus meticulous management to avoid lethal complications inherent in individual prostheses. Assessment of functional durability of hemodynamically adequate valve designs requires long-term evaluation.

Decisions for therapy of heart disease caused by an abnormal aortic valve are based upon current knowledge of the natural history of the valve affliction, the hemodynamic abnormalities and the cineangiographic visualization of cardiac anatomy. Despite advances in technology and knowledge of aortic valve disease, controversy surrounding the timing of valve replacement has persisted because the life history of patients with an aortic valve prosthesis may not have achieved expectations or, in some instances, significant improvement over the course of the "surgically untreated" disease.[1] For valve replacement to be beneficial, patients must survive the operation with symptomatic relief and progress to an acceptable level of rehabilitation. Longevity must not be skewed by transvalve gradients, thromboembolism, bleeding from anticoagulation therapy or late dysfunction of the prosthetic device. These events may influence regression or progression of the cardiac pathophysiologic state caused by the original valve deficiency.

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TABLE I

Patient Population and Preoperative Characteristics

	Valve Lesion			Total	
	AS	AR	Mixed	no.	%
Total group (no. patients)	88	95	58	241	100
Sex					
Male	56	64	43	163	68
Female	32	31	15	78	32
Age (yr)					
Range	13–69	12–72	20–70	12–72	...
Mean	49	41	48	46	...
Preoperative characteristics					
NYHA I–II	15	21	7	43	18
NYHA III–IV	73	74	51	198	82
Congestive heart failure	45	76	40	161	67
Angina (chronic)	54	24	33	111	46
Syncope (recurrent)	41	8	16	65	27
Previous myocardial infarction	22	10	12	44	18
Endocarditis	2	15	6	23	10
Previous valve operation	6		3	9	4

AR = aortic regurgitation; AS = aortic stenosis; Mixed = mixed aortic and aortic and mitral lesions; NYHA = New York Heart Association functional classification.

During the early years of valve surgery at our institution, indications for aortic valve replacement were determined almost invariably by the severity of symptoms. Many patients were referred because of progressive heart failure, recurrent syncope or angina. Current indications for surgery reflect detailed analysis of a comprehensive hemodynamic evaluation. Thus, patients with aortic stenosis are evaluated for valve replacement when they first manifest electrocardiographic evidence of left ventricular strain, syncope or the most subtle signs of left ventricular dysfunction before the appearance of advanced signs of cardiac decompensation. The aortic transvalve gradient is often in excess of 50 mm Hg at rest. Similarly, patients with severe aortic regurgitation now receive the same critical analysis of hemodynamic function. They are considered for surgery at the first sign of progression of left ventricular enlargement and diminishing exercise tolerance before the onset of disability and the occurrence of frank left ventricular failure.

The evaluation of aortic valve replacement cannot be complete without comparison of the course of surgically treated versus surgically untreated disease. This comparison is made possible only with prospective randomized study for which justification no longer exists. Comparison of published data can be misleading because of failure to define patient material and lack of uniform methods of data analysis.[2] If one assumes that all surgical survivors are identical for the sake of comparing surgically treated and untreated patients one oversimplifies the problem. This assumption does not account for vast differences and continuing modifications in valve design that might influence the risk of embolism, hemolysis, transvalve gradients and other factors. Each new development is followed by numerous reports of early results. However, knowledge of the impact of prosthetic valves on cardiac valve disease will come only from extended follow-up studies of the life history of patients and their individual prostheses.

Surgical replacement of diseased heart valves has created a generation of patients with prosthetic valves of many years' duration whose care is made complex by the variety of complications caused by differences in valve design. An increasing number of patients are in their second decade of life with the original artificial valve still in place. This group of patients deserves close attention for assessing durability of the prosthesis. As a group, these patients will provide experience for increasing the reliability of noninvasive techniques for evaluating prostheses. The specific preoperative characteristics, prosthetic designs and postoperative course associated with extended life and successful rehabilitation can be helpful in determining the optimal criteria for time of operation and selection of prosthesis.

This report is based on a long-term examination of 241 consecutive patients who underwent isolated aortic valve replacement at the Medical College of Georgia between 1963 and 1976 and were followed up through January 1977. Prosthesis-related survival rates, complications, rehabilitation and late clinical characteristics of six valve types are emphasized.

Patients and Methods

Patients: A retrospective review was made of all patients who received an aortic valve prosthesis since the start of the valve replacement program at this institution in 1963. Of a total of 241 patients, 163 were male and 78 were female (Table I). The mean age at operation was 46 years (range 12 to 72).

Aortic valve hemodynamic lesions were designated aortic stenosis and aortic regurgitation according to previously established criteria.[3] Aortic stenosis was defined as severe aortic stenosis with 1+ or less aortic regurgitation; aortic regurgitation was defined as severe regurgitation accompanied by a peak systolic left ventricular outflow gradient of less than 25 mm Hg. The hemodynamic lesion was aortic stenosis in 88 patients (37 percent) and aortic regurgitation in 95 (39 percent). Combined lesions with fixed orifice aortic stenosis and aortic regurgitation, or both aortic and mitral valve disease, were present in 58 (24 percent).

The origin of the valve disease was rheumatic in 42 percent. Congenital bicuspid valves were discovered in 24 percent, atherosclerotic valves in 8 percent and syphilitic aortitis in 5 percent. Trauma and other or unknown causes resulted in an aortic valve lesion in 21 percent.

The preoperative conditions of the 241 patients are shown in Table I. Chronic congestive heart failure had been treated preoperatively in 161 patients (45 with aortic stenosis, 76 with regurgitation and 40 with mixed lesions). Sixty-five patients (41 with aortic stenosis, 8 with regurgitation and 16 with mixed lesions) had had several episodes of syncope. Preoperative endocarditis occurred in 23 patients. Nine had had a previous aortic commissurotomy or open valvuloplasty. One hundred ninety-eight (82 percent of the group) were severely symptomatic, and were classified in New York Heart Association functional class III or IV[4] before operation. The presence of third and fourth heart sounds or a paradoxically split or absent second heart sound was not always reliably recorded.

Forty-three patients (18 percent) in functional classes I and II underwent aortic valve replacement for various urgent reasons other than heart failure. These were antibiotic-resistant endocarditis, severe regurgitation due to rheumatic valvulitis, trauma or syphilis with rapidly increasing heart size, the appearance of angina or a pattern of left ventricular strain

TABLE II

Experience With Isolated Aortic Valve Replacement in 241 Patients

	Valve Model						
	1000	1200	2300	2310	2320	Bjork-Shiley	Totals
Dates in use	'63–'66	'66–'68	'68–'69	'69–'71	'71–'74	'72–'76	1963–76
Procedures (no.)	35	33	30	24	53	66	241
Operative survivors	30	30	27	21	43	61	212
Late cardiac deaths	16	11	17	10	7	7	68
Withdrawn for cause*	5 aabcd	5 abccc	2 ad	2 cc	5 aacdd	1 b	20 ...
Long-term survivors	9	14	8	9	31	53	124
Average valve-related cardiac mortality rate (percent/year)	4.8	3.6	7.1	6.1	3.7	4.0	4.0

* Withdrawn from actuarial analysis at time of (a) replacement of aortic valve prosthesis (6 cases); (b) addition of mitral valve prosthesis (3 cases); (c) noncardiac death due to malignancy (5 cases), auto accident (1 case), suicide (1 case) after an average of 5 years observation; (d) loss to follow-up (4 cases).

in the electrocardiogram. These patients differed from the rest of the group in several ways: they were younger (mean age 39 years) at operation; they had a higher incidence rate of aortic regurgitation (49 percent), a lower incidence rate of mixed valve lesions (16 percent) and only a 2 percent incidence rate of atherosclerotic valve disease.

Operative technique: In all cases, valve replacement was accomplished with median sternotomy exposure and various conditions of extracorporeal circulation. Early in the clinical program normothermic perfusion was employed utilizing a disc oxygenator primed with whole blood collected in ACD solution. Later in the series, the standard technique for cardiopulmonary bypass was hypothermic perfusion with hemodilution priming and a bubble oxygenator. In most cases one or both coronary arteries were perfused. Before discharge from the hospital, most patients were placed on anticoagulant therapy with warfarin.

Prostheses used: Successive generations of Starr-Edwards prostheses were implanted (Table II). In 1972, the Bjork-Shiley tilting disc valve was introduced into the series. Initially the Bjork-Shiley prosthesis was chosen for insertion into patients with a narrow aortic root. At present, it is used according to individual preference of the surgeon.

Statistical analysis: The life table method[5] was used to analyze (1) survival, (2) occurrence of complications in general, (3) occurrence of embolic phenomena in particular, (4) survival according to hemodynamic lesion, and (5) survival according to preoperative New York Heart Association functional classification. Operative mortality (summarized in Table III) is excluded from actuarial display because our purpose is to compare late complications and survival by valve model. Only four of the operative survivors could not be located when the study was closed, giving a 98 percent follow-up rate. The complication curves are derived from the first occurrence of a serious complication such as congestive heart failure, thromboembolism, hemolysis, periprosthetic leak, acute myocardial infarction, endocarditis or ball variance, as listed in Table IV. Annual valve-related cardiac mortality rate was calculated from the actuarial analyses of individual valve groups: The cumulative mortality was divided by the number of years of follow-up, including all patients until withdrawn for cause or death. The level of rehabilitation was carefully reviewed in 124 patients with current follow-up data to January 1977.

Results

Operative deaths: Twenty-nine (12 percent) of the 241 patients studied died within 30 days of operation. Autopsies were performed in 21. The causes of operative death are shown in Table III. The operative risk was known to be high in 19 of these patients: 10 were in functional class IV, 12 had left ventricular end-diastolic pressures greater than 20 mm Hg, 3 had bacterial endocarditis, 2 had syphilitic valve and aortic disease and 1 had acute rheumatic fever.

Late deaths: Sixty-eight of 212 operative survivors died of cardiac causes 1 month to 9 years after operation. The average annual valve-related cardiac mortality rate for the entire group was 4 percent.

Table II summarizes the total experience by valve model. Twenty patients were withdrawn from actuarial analysis at the time an event interrupted evaluation of their aortic valve prosthesis: 6 of the 20 had the original prosthesis replaced, 3 had a mitral valve prosthesis added, 5 died of malignancy, 1 died after an automobile accident, 1 committed suicide and 4 were lost to follow-up. Therefore, all mortality rates are related to problems with the prosthesis or other cardiac causes.

The annual valve-related cardiac mortality rate ranged from 3.6 to 7.1 percent (average 4 percent). Rates among the earlier model 1000 and 1200 series (4.8 and 3.6 percent, respectively) were lower than in patients receiving the model 2300 and 2310 prostheses, the first

TABLE III

Causes of Operative Death in 29 Patients

Cause	no.
Low cardiac output	16
Technical	5
Infection	4
Sudden and unexplained	2
Arrhythmia	1
Cerebrovascular accident	1

TABLE IV

Complications and Late Deaths* in 212 Operative Survivors

	Valve Model						
	1000	1200	2300	2310	2320	Bjork-Shiley	All Valves
Operative survivors (no.)	30	30	27	21	43	61	212
Sudden unexplained death	(1)	(3)	(4)	(4)	(3)	(1)	(16)
Congestive heart failure	11 (6)	6 (2)	13 (7)	5 (5)	5 (1)	7	47 (21)
Bleeding due to anticoagulation†	9	7 (1)	7	2	1	2 (1)	28 (2)
Thromboembolism	4 (1)	6 (2)	4	3 (1)	7	2 (2)‡	26 (6)
Uncontrolled hemolysis	5	5	7	2	3	2	24
Periprosthetic leak	5 (1)	4	2 (1)	1	5 (1)	4	21 (3)
Acute myocardial infarction	4 (2)	3 (2)	5 (3)	3	3	1	19 (7)
Endocarditis	3 (1)	...	2 (1)	...	2	4 (1)	11 (3)
Ball variance	7 (4)	...	...	...	...	...	7 (4)
Cloth wear	...	...	...	...	2 (2)	...	2 (2)
Dissecting aortic aneurysm	...	...	...	...	...	1 (1)	1 (1)
Mycotic aortic aneurysm	...	...	...	...	...	1 (1)	1 (1)
Reoperation§	5	4 (1)	2 (1)	...	4	2	17 (2)
Total late deaths	(16)	(11)	(17)	(10)	(7)	(7)	(68)

* Deaths in parentheses indicate primary cause.
† Only uncontrolled bleeding in two patients included in actuarial analysis.
‡ Thrombosed valves without peripheral thromboembolism.
§ Not included in actuarial analysis.

generations of cloth-covered valves (7.1 and 6.1 percent). The annual valve-related cardiac mortality rate among patients receiving model 2320 was approximately 3.7 percent, with the longest follow-up approaching 6 years. The annual valve-related cardiac mortality rate of the Bjork-Shiley valve was 4 percent. Table IV lists the causes of valve or cardiac complications and deaths in the 212 operative survivors. Autopsy confirmed the cause of death in 21 patients. Hospital records, death certificates, referring physicians and family members supplied information for assessing the cause of death in the remaining 47 patients.

Survival and complications by valve model: *Starr-Edwards model 1000 (30 operative survivors) (Fig. 1):* Ball variance occurred only in this model. Sudden death from variance occurred in four patients 5, 6, 8 and 9 years, respectively, after implantation. The poppet was replaced in another three patients when variance was detected. Thirty-eight percent of the group survived 13 years, but the majority of survivors (75

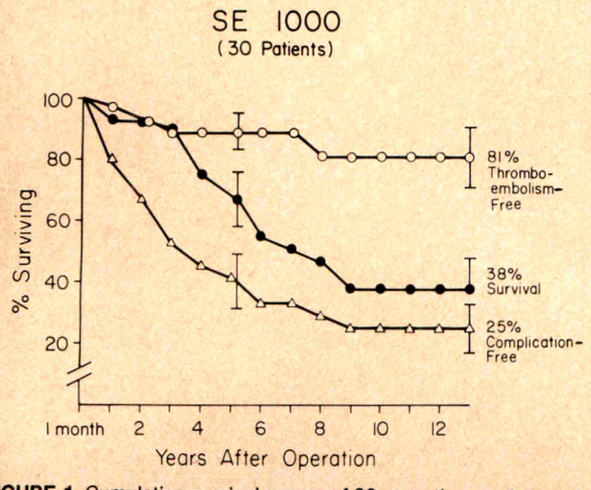


FIGURE 1. Cumulative survival curves of 30 operative survivors who received a Starr-Edwards (SE) model 1000 valve. (Data from one patient who died of noncardiac causes withdrawn. See Table II.)

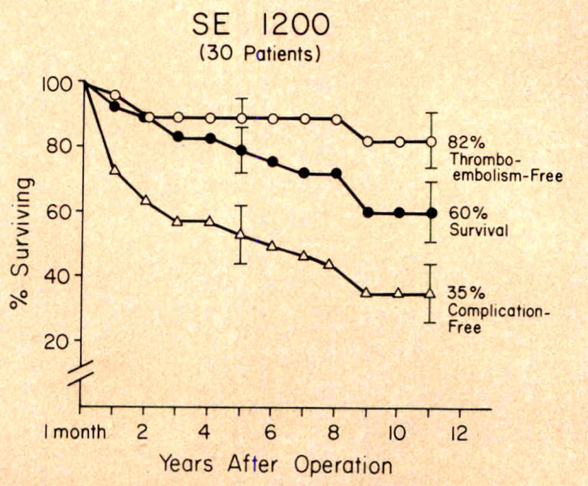


FIGURE 2. Cumulative survival curves of 30 operative survivors who received a Starr-Edwards (SE) model 1200 valve. (Data from three patients who died of noncardiac causes withdrawn.)

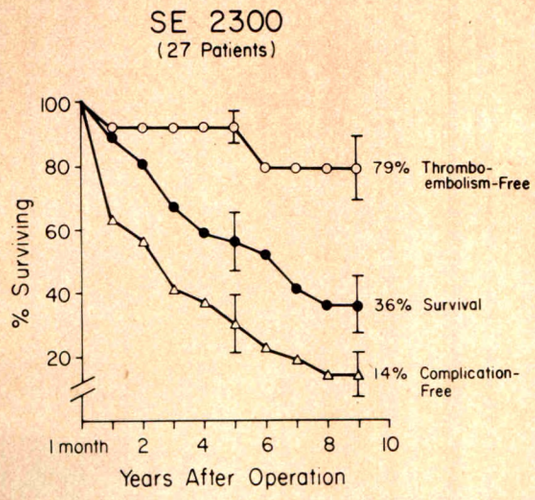


FIGURE 3. Cumulative survival curves of 27 operative survivors who received a Starr-Edwards (SE) model 2300 valve.

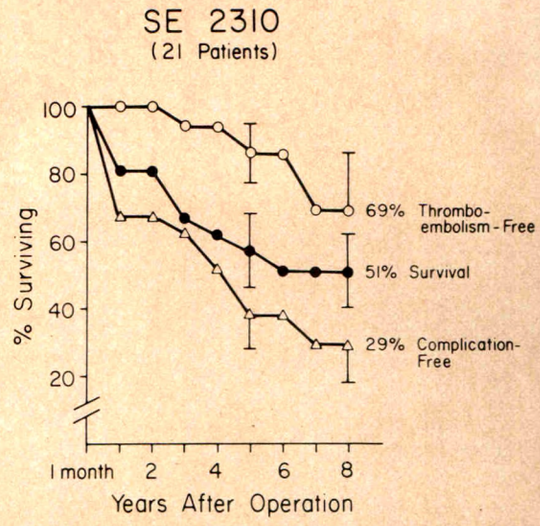


FIGURE 4. Cumulative survival curves of 21 operative survivors who received a Starr-Edwards (SE) model 2310 valve. (Data from two patients who died of noncardiac causes withdrawn.)

percent) had a variety of prosthesis-related disorders or progressive heart disease (Table IV). Eighty-one percent of the operative survivors are free of embolism. Hemolysis was related to periprosthetic leak in two patients, ball variance in two and a transvalve gradient of 41 mm Hg in one.

Starr-Edwards 1200 (30 operative survivors) (Fig. 2): Patients with this prosthesis had the lowest valve-related cardiac mortality rate although complications have continued to occur (Table IV). Four reoperations were necessary to repair periprosthetic leaks that were causing severe hemolysis; one reoperation was fatal. Two sudden deaths in patients who had no previous complications caused the sudden drop in the curves during the 9th year, and 60 percent of patients are surviving at 11 years.

Starr-Edwards 2300 (27 operative survivors) (Fig. 3): Only 36 percent of patients in this group have survived up to 9 years. Although 79 percent of these patients have been free of embolism for up to 9 years, only 14 percent have been free of complications (Table IV). The leading causes of morbidity have been congestive heart failure, acute myocardial infarction, hemolysis and thromboembolism. Twelve patients were recatheterized, and gradients of 6 to 70 mm Hg (mean 35) were measured across the prosthesis. Of seven patients with a transprosthetic gradient of 27 to 70 mm Hg, four had hemolysis (two died suddenly, two are living). Sudden unexpected death occurred in four patients, three with a measured gradient of 54, 60 and 60 mm Hg, respectively.

Starr-Edwards 2310 (21 operative survivors) (Fig. 4): Five of 10 deaths in this group were due to congestive heart failure. Four other deaths were sudden and unexpected (Table IV). Hemolysis was caused by a slightly leaking prosthesis in one patient, and the other patient with hemolysis refused restudy and later died of a cerebrovascular accident. The close correspondence of the complication and survival curves is noteworthy because late major complications were frequent and only 51 percent of the original group have survived to 8 years.

Starr-Edwards 2320 (43 operative survivors) (Fig. 5): In the 6th year of follow-up, 78 percent of patients in this group survive. Only 82 percent are embolism-free; the rate of embolism was highest with this valve model because of recurrences in several patients (Table V). Strut cloth wear culminated in sudden death in two (possibly three) patients. A perivalve leak developed in five patients and was repaired successfully in three. Congestive heart failure in five, severe hemolysis caused by leak in one and of unknown origin in two and two cases of infected valves leave 59 percent of the operative

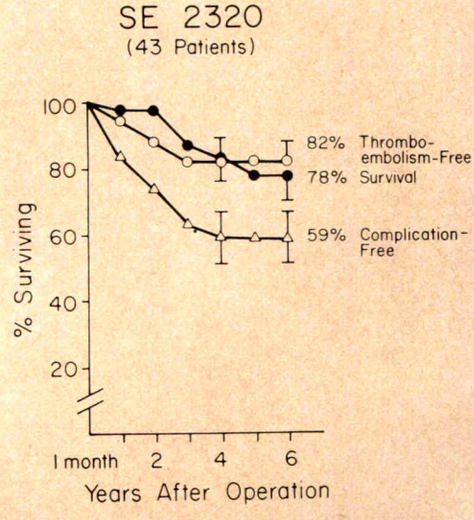


FIGURE 5. Cumulative survival curves of 43 operative survivors who received a Starr-Edwards (SE) model 2320 valve. (Data from one patient who died of noncardiac causes withdrawn.)

TABLE V

Thromboembolic Complications in 212 Operative Survivors

	Valve Model						
	1000	1200	2300	2310	2320	Bjork-Shiley	All Valves
Total patient years follow-up	196	213	139	92	153	142	935
Thromboembolic episodes	6*	7	4	3	11	(2†)	31
Episodes/100 patient years	3.1	3.3	2.9	3.3	7.2	. . .	3.3
Fatal	1	2	. . .	1	. . .	. . .	4
Residual	1	. . .	1	1	2	. . .	5

* One patient had multiple uncounted episodes in the year before death due to cerebrovascular accident.
† Two valves thrombosed but produced no peripheral thromboemboli. Not included in thromboembolism-free curve.

survivors in this valve replacement group free of complications (Table IV).

Björk-Shiley (61 operative survivors) (Fig. 6): No instances of symptomatic peripheral thromboembolism were observed. However, two valves thrombosed, causing intractible congestive heart failure and death. Eighty percent of the operative survivors have survived to 5 years; 68 percent are free of complications (Table IV). Two perivalve leaks were repaired successfully, and one patient with deteriorating cardiac function and a leaking prosthesis has refused restudy and repair. Five other patients have short early diastolic murmurs without functional abnormality and are not included in the actuarial analysis of complications. Hemolysis was corrected in one patient with repair of leak; its cause is not obvious in another. Four patients had bacterial endocarditis, and one had an acute myocardial infarction that occurred during an episode of bacterial endocarditis.

Survival by hemodynamic lesion: Survival rates from life table analysis according to each hemodynamic lesion are shown in Figure 7. Sixty-six percent of patients whose valve lesion was aortic stenosis survive, compared with only 30 percent whose valve lesion was aortic regurgitation ($P < 0.01$). The differences in survival are not great during the early years but become more pronounced in patients who have had prosthetic valves for a longer duration.

Survival according to preoperative functional classification (Fig. 8): Forty-two of the 212 operative survivors were in functional class I or II at the time of operation, and 91 percent of these are current survivors up to 13 years. Of 144 patients who were in class III at operation, 39 percent have survived up to 13 years. The difference between survival rates in combined classes I and II and in class III is highly significant ($P < 0.001$). Twenty-six patients were in class IV at operation and, although 51 percent survived up to 8 years, none survived longer than 9 years although most were initially relieved of symptoms. The annual valve-related cardiac mortality rate for the first 5 years in the operative survivors was 1.8 percent for patients in classes I and II, 6.4 percent for those in class III and 9.8 percent for those in class IV.

Thromboembolism: Thirty-one thromboembolic episodes were recorded in 24 patients; 4 were fatal (Table V). Five patients are living with residuals of strokes. The group with the model 2320 prosthesis leads in frequency of thromboembolism (7.2 episodes/100 patient years). Embolic phenomena occurred with a consistent frequency in the other valve groups (2.9 to 3.3 episodes/100 patient years). Anticoagulation was

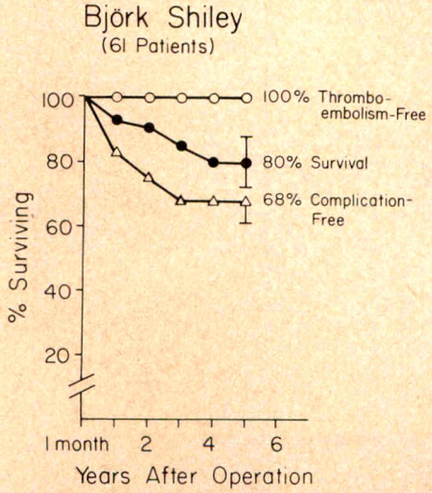


FIGURE 6. Cumulative survival curves of 61 operative survivors who received a Bjork-Shiley tilting-disc valve.

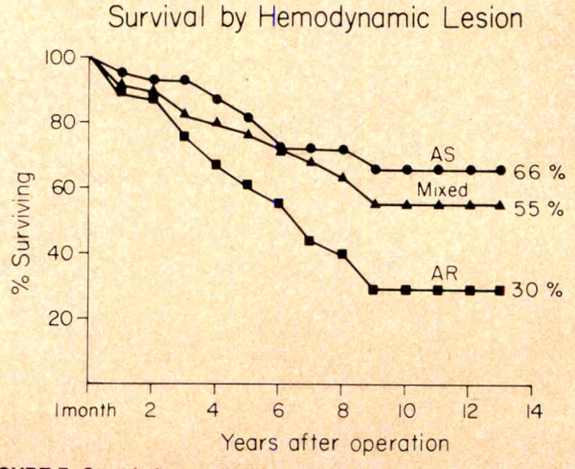


FIGURE 7. Cumulative survival curves of 212 operative survivors by hemodynamic lesion. AR = aortic regurgitation; AS = aortic stenosis; Mixed = mixed aortic and aortic and mitral lesions.

TABLE VI

Hemolysis and Related Factors

	Valve Model						
	1000	1200	2300	2310	2320	Bjork-Shiley	All Valves
Hemolytic anemia (no. patients)	5	5	7	2	3	2	24
Periprosthetic detachment/hemolysis control with reoperation	2/2	4/3*	...	1/*	1/1	1/1	9/7
Ball variance/ hemolysis control with reoperation	2/2	...	...	...	...	...	2/2
Restudied/elevated transvalve gradient	4/4	...	5/5	1/1	...	...	10/10
Cause of hemolysis unknown	...	1	2	1	2	1	7

* Two patients died, one at reoperation, and one of suicide.

known to be inadequate at the time of the embolic episode in 15 (62.5 percent) of these patients.

Reoperation: Reoperation was necessary in 17 patients: for ball variance in 3, perivalve leak in 10, uncontrollable hemolysis in 2 and endocarditis with prosthetic disruption in 2.

Hemolysis: Table VI provides data on the 24 patients in whom hemolysis required control. When periprosthetic detachment in nine patients was detected and repaired, seven patients continued to have normal hemoglobin levels and two patients died, one at reoperation and one of suicide. Replacement of two deformed poppets in model 1000 valves was followed by normal hemoglobin values. Ten patients who had hemolysis and were recatheterized for recurrence of symptoms had transvalve gradients of 25 to 70 mm Hg (mean 43.5). In seven patients no obvious cause for hemolysis has been found, and iron therapy maintains hemoglobin levels near normal.

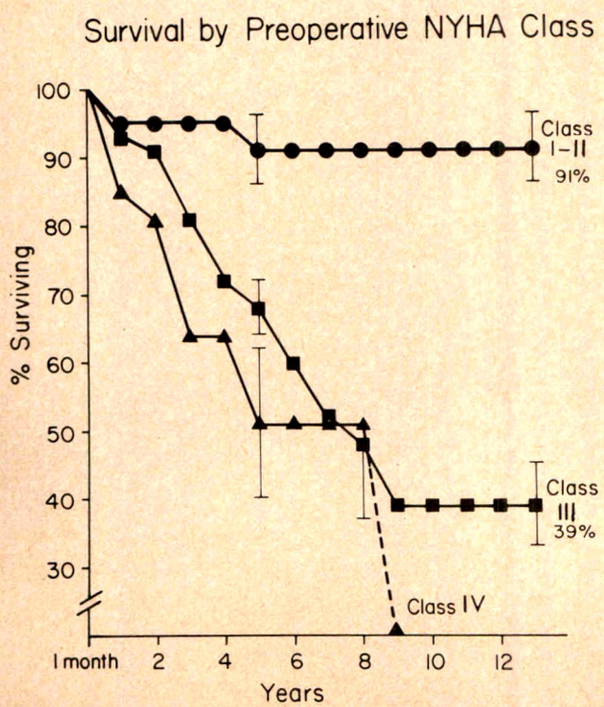


FIGURE 8. Cumulative survival curves of 212 operative survivors by preoperative New York Heart Association (NYHA) functional classification.

Repeat cardiac catheterization: Table VII lists pertinent findings in 41 patients who underwent restudy for specific indications. Resting transvalve gradients of more than 20 mm Hg were found in 20 patients with models 1000, 1200, 2300 and 2310. Sudden unexpected death occurred in three patients who had high transvalve gradients (54, 60, 60 mm Hg, respectively) across model 2300 valves, sizes 8, 10 and 10, respectively. Hemolysis accompanied an elevated gradient in nine patients.

Functional rehabilitation: In January 1977, of 124 survivors, 101 were leading active and normal lives, 5 considered themselves unemployable in their preoperative job although persistent symptoms of heart disease were mild and 10 others were active although they had symptoms with some exercise limitation. Serious limitation was related to two prostheses, a model 2300 with a transvalve gradient of 70 mm Hg and a model 2310 with a gradient of 49 mm Hg. Five patients had

TABLE VII

Resting Transprosthetic Pressure Gradients in 41 Patients Restudied for Recurrent Symptoms or Congestive Heart Failure (19), Possible Ball Variance (10), Hemolysis (6) or Leak (6)

	Valve Model					
	1000	1200	2300	2310	2320	Bjork-Shiley
Number restudied	9	7	12	7	4	2
Gradients > 20 mm Hg (no. patients)	5	5	7	3	0	0
Resting gradient (mm Hg)						
Mean	27	24	35	25	5	0
Range	6–44	6–35	6–70	9–49	0–13	0

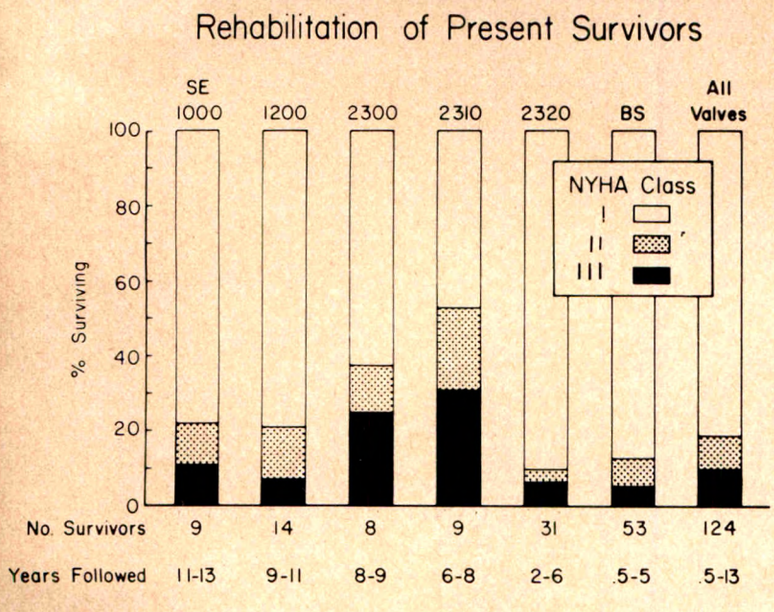


FIGURE 9. Rehabilitation of 124 current survivors of aortic valve replacement followed up from 0.5 to 13 years after operation. BS = Bjork-Shiley; NYHA = New York Heart Association functional classification; SE = Starr-Edwards.

progressive cardiac disease due to severe hypertension in one (model 1000), mitral valve disease in one (model 2300), alcoholic cardiomyopathy in one (model 2320) and of undetermined causes in two (models 1200 and 2310). One patient was disabled because of residuals of a perioperative cerebrovascular accident (model 2310).

Figure 9 summarizes the results according to functional classification after operation. Functional rehabilitation was related to valve model and not to time after implantation. Rehabilitation was poorest with the model 2300 and 2310 valves.

Discussion

Aortic stenosis: Indications for surgery in aortic valve disease are much easier to discern for aortic stenosis than for aortic regurgitation. The average survival time of 1 1/2 to 3 years for patients with syncope, angina and degrees of left heart failure due to aortic stenosis is a compelling reason for valve replacement.[6] In a small group of adult patients with medically treated aortic stenosis, 48 percent survived 5 years and only 10 percent survived 10 years.[7] Figure 7 shows 66 percent survival rate in 13 years in our group of patients with aortic stenosis. Fourteen of 15 with aortic stenosis who were in functional class I or II at operation are still living up to 13 years after operation.

Aortic regurgitation: Eighty to 90 percent of patients with moderate aortic regurgitation can be expected to survive 10 years or more with medical management.[8,9] However, medically treated hemodynamically severe regurgitation with minimal symptoms is associated with a 75 percent 5 year survival rate and a 50 percent 10 year survival rate after diagnosis.[6] As cardiac decompensation and angina pectoris ensue, not only does the prognosis worsen rapidly but also surgical survival decreases and the long-term results of surgery may be jeopardized.[6,8,10] The decision to operate on an incompetent aortic valve once was based on the severity of symptoms, but the heart is irreversibly damaged by the time symptoms are severe in aortic regurgitation. If valve replacement can be offered before development of congestive heart failure, survival and rehabilitation can be improved significantly. Figure 7 shows that our patients with aortic regurgitation had a 30 percent survival rate in the 13th year. However, 72 percent (13 of 18) with aortic regurgitation who underwent valve replacement for reasons other than congestive heart failure are alive up to 13 years after operation. Only 47 percent (35 of 74) with regurgitation complicated by congestive failure are current survivors. Eighty-four percent (16 of 19) with regurgitation operated on while in functional class I or II are alive, compared with only 42 percent (30 of 71) with regurgitation that progressed to functional class III and IV. (Five patients with aortic regurgitation are not included in these calculations, having been withdrawn from analysis because of replacement of the prosthesis or loss to follow-up.)

Preoperative condition and survival: Eighty percent of the patients in this series were severely symptomatic at operation (Table I). Our analysis revealed no statistically significant relations between specific symptoms or symptom complexes and patient survival. Data from the catheterization laboratory were not helpful in predicting outcome of valve replacement. Our series was too small for discrimination by hemodynamic abnormalities and specific symptoms or syndromes. The 91 percent long-term survival rate among patients in functional class I and II suggests that surgery should be offered before disabling cardiac symptoms develop (Fig. 8).

Complications and survival: In addition to valve lesion and stage of disease, long-term survival depends upon incidence of late complications, which in turn depends on the valve model implanted. Early postoperative results in our series indicated that most survivors were symptomatically better 1 year after operation, according to their functional classification. Congestive

heart failure has been the most frequent complication, especially in the early models of the Starr-Edwards valves with close cage to poppet clearances. This problem was commonplace in models 2300 and 2310 valves with the addition of cloth to the struts. Sudden unexplained death, presumably due to arrhythmia, congestive heart failure or valve malfunction, occurred in 16 patients from 1 month to 9 years after operation, and was most frequent in the 1200, 2300 and 2310 model groups. Sudden death due to ball variance in the model 1000 valve was essentially eliminated with improvement of the Silastic® composition of the poppet.

High transvalve resting gradients found during a number of repeat cardiac catheterizations (Table VII) probably account for the disturbing progression of cardiac pathophysiologic state in many of the patients with the early Starr-Edwards valves, particularly models 2300 and 2310. Unfortunately, the influence of exercise on gradient was not tested during restudy. The current generation of prostheses appears to have eliminated some of the unmanageable obstructive hemodynamic properties inherent in earlier designs. An insignificant transvalve gradient in the wide clearance caged ball (model 2320) and tilting disc prostheses relieves obstruction at the level of the prosthesis and consequent progression of cardiac disease (Table VII).

Hemolysis appears to be related to high transvalve gradients in the early Starr-Edwards valves. Ball variance in two patients and periprosthetic detachment in nine also contributed to hemolytic anemia. Although iron therapy may control the anemia, the appearance of this complication might suggest a closer assessment of durability of the prosthesis. Hemolysis has not been a significant problem in patients with wide clearance caged ball or tilting disc valves.

Since the demonstration of cloth wear in the model 2320 prosthesis, we have used the model 2400, of similar configuration but with metal contact surfaces on the struts. The model 2320 valve is hemodynamically reliable.[11] However, cloth wear on the struts may be the cause of sudden death and peripheral emboli that have occurred at the rate of 7.2 episodes/100 patient years (Table V). Anticoagulation has been used in almost all patients. Nearly two thirds of thromboembolic episodes occurred during periods when anticoagulation had to be terminated or was poorly controlled. Inadequate anticoagulation remains a more frequent problem than bleeding due to warfarin overdose. Twenty-eight episodes of bleeding and two deaths in the entire group were due to inadequate anticoagulation. The need for anticoagulation continues to be a serious disadvantage of all prostheses that we have implanted.

Clinical implications: Survival after implantation of the early model caged ball prostheses (Starr-Edwards models 1000, 1200, 2300 and 2310) appears to have been a compromise between relief from the original symptoms of aortic valve disease and complications related to the prostheses. Early results in patients receiving Starr-Edwards model 2320 and Bjork-Shiley prostheses seemed considerably better until the appearance of recurrent thromboembolism in the group with model 2320 and thromboses of two small Bjork-Shiley valves (Fig. 5 and 6). Strut cloth wear is an evolving problem with the model 2320 prosthesis. Despite thrombosis of the two Bjork-Shiley valves, peripheral thromboemboli are infrequent. Absence of significant transvalve gradients in these two valves seems to indicate that persistent congestive heart failure recorded in 12 patients is due to preoperative cardiac disease. Thus, after 6 years of experience with the model 2320 and Bjork-Shiley prostheses, complications appear to be fewer in frequency and more manageable. Nevertheless, late thromboembolism or loss of normal prosthetic sounds in patients with either valve indicates that close investigation is required to determine the need for replacement of the prosthesis.

Our overall experience indicates that long-term results should improve if surgery can be offered at an earlier stage of aortic valve disease. Perhaps more attention should be accorded the earliest signs of myocardial decompensation, namely, evidence of progressive left ventricular enlargement, ischemia or strain in the electrocardiogram or decreasing exercise tolerance in the treadmill stress test, despite lack of other more compelling symptoms. Generally, patients with the late 2320 and Bjork-Shiley models were operated on at an earlier stage. Their level of functional rehabilitation appears better than that of the earlier groups (Fig. 9). Long-term survival was best in patients in functional classes I and II (Fig. 8). Of the 124 long-term survivors, 101 are enjoying complete rehabilitation. Seventy-nine patients are employed (8 in spite of mild symptoms), 30 are retired or unemployed without exercise limitations and 15 are disabled because of exercise limitation.

High transvalve gradients in long-term survivors with close clearance Starr-Edwards valves are the source of some lasting management problems. Despite the threat of sudden death, some patients continue to function well. Others are plagued by progressively deteriorating left ventricular function (Fig. 9). The recommendation to replace any prosthesis suspected of malfunction remains difficult but is perhaps the only reasonable approach. Echocardiographic examination can diagnose obstruction by thrombus, poppet malformation and diminished orifice size. At present in our institution, we do not rely solely upon echocardiographic evidence of prosthetic malfunction.

The rising popularity of new modifications of old valve designs and bioprostheses underscores the continuing requirement for long-term prospective studies in excess of 5 years. Such studies remain the cornerstones for assessing the reliability and durability of prosthetic materials. Long-term postoperative management of patients with an aortic valve prosthesis must be tailored to the known characteristics of the implanted valves.

Acknowledgment

Ms. Wanda Rice prepared the data and manuscript. Rollie J. Harp, MS, Assistant Professor of Health, Systems, and Information Sciences, Division of Systems and Computer Services of the Medical College of Georgia, provided the actuarial analyses.

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Muscle Fiber Disarray in Common Heart Diseases

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Myocardial fiber disarray was found at necropsy in each of 53 hearts, 33 from patients with cardiovascular disease—systemic hypertension (12 patients), coronary heart disease (17 patients) or cor pulmonale (4 patients)—and 20 from patients with a normal heart. The myocardial fiber disarray was of mild degree in all 53 patients and, although similar to that observed by others in hearts of patients with hypertrophic cardiomyopathy, the amount of myocardial fiber disarray per heart was considerably less than that observed in patients with hypertrophic cardiomyopathy.

Myocardial fiber disarray has been described as the histologic feature of idiopathic hypertrophic cardiomyopathy with or without subaortic stenosis.[1–11] However, it is not specific for this condition because it has been found, although to a lesser extent, in the heart of patients with idiopathic cardiomyopathy of the dilated type, alcoholic cardiomyopathy and various congenital heart diseases including tetralogy of Fallot and ventricular septal defect.[5,8,9] The frequency of myocardial fiber disarray has not been studied in an adequate number of persons with a clinically normal heart or in patients with such common diseases as arteriosclerotic, hypertensive and pulmonary heart disease. This paper therefore describes the frequency of myocardial fiber disarray in these conditions and in clinically normal hearts studied at necropsy.

Material and Methods

Cases: The hearts of 53 adults studied at necropsy were selected from a total of approximately 280 autopsies performed between July 1975 and May 1976 at the University of Cincinnati College of Medicine. The age of the 53 patients ranged between 28 and 97 years (average 62 years). There were 23 men and 30 women, 31 whites and 22 blacks. The heart weights ranged between 180 and 530 g (average 344 g) (Table I). During the selection of specimens for study, a heart was judged normal if there was no evidence of clinical heart disease, the coronary arteries exhibited less than 50 percent luminal narrowing and there was no significant valve disease. Except in the normal group, the heart weight was more than 350 g in women and more than 400 g in men. In the group with arteriosclerotic heart disease, the luminal narrowing of extramural coronary arteries by atherosclerosis was greater than 75 percent. The degree of grossly apparent luminal narrowing was recorded (in percent) after transection of the vessels at 5 mm intervals. Regardless of the presence of significant atherosclerosis, a case was included in the hypertensive group whenever there was a clear-cut history of hypertension or treatment of hypertension (diastolic pressure 90 mm Hg or more, and systolic 140 or more).[12] All hearts of patients with cor pulmonale had a hypertrophied right ventricle. The anatomic criteria for cor pulmonale established by others[13–15] were utilized. Of the 12 patients with systemic hypertension, 9 were aged 60 or more years and 4 of these also had significant coronary atherosclerosis (75 percent or more luminal narrowing). Of these 12 patients, 4 had end-stage renal disease. All 12 hearts in this group had left ventricular hypertrophy, and 4 also had severe right ventricular hypertrophy from severe

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pulmonary disease. Of the 20 normal subjects, 5 were less than age 40 years and 9 were less than age 50 years.

One case of idiopathic hypertrophic cardiomyopathy was utilized as a control case. The anatomic criteria for idiopathic hypertrophic cardiomyopathy as described by others[5,9] were utilized. This patient did not have systemic hypertension. The heart weighed 800 g.

Histologic examination: All hearts were fixed in 10 percent buffered formalin for a minimum of 48 hours. The ventricles were then sliced parallel to the coronary sinus at 1 cm intervals. The entire heart slices were manually dehydrated with acetone and infiltrated and embedded in paraffin. Several giant histologic sections of 7 to 9 μ thickness were obtained from each slice by using the Jung sliding microtome (Fig. 1, diagram). Hematoxylin-eosin and Masson's trichrome stains were utilized to identify myocardial fiber disarray and degree and extent of interstitial fibrosis. Myocardial fiber disarray and interstitial fibrosis were recorded on a schematic drawing of the sliced ventricles. In this study, any deviation from the parallel arrangement was considered aberrant except that

TABLE I

Summary of Cases

Group	Cases (no.)	Age (yr) Range	Age (yr) Average	Heart Weight (g) Range	Heart Weight (g) Average	Race Black	Race White
Normal*	20	28–97	57	180–370	284	9	11
Hypertension	12	30–94	67	380–530	434	7	5
ASHD	17	40–94	65	215–500	328	2	15
Cor pulmonale	4	47–70	62	365–510	436	4	0
Total	53	28–97	62	180–530	344	22	31

* This group included two patients with a low heart weight. Both had a malignant neoplasm with widespread involvement. Their heart showed infiltration by malignant tumor cells. There was no clinical evidence of cardiac impairment or other significant cardiac disease.
ASHD = arteriosclerotic heart disease.

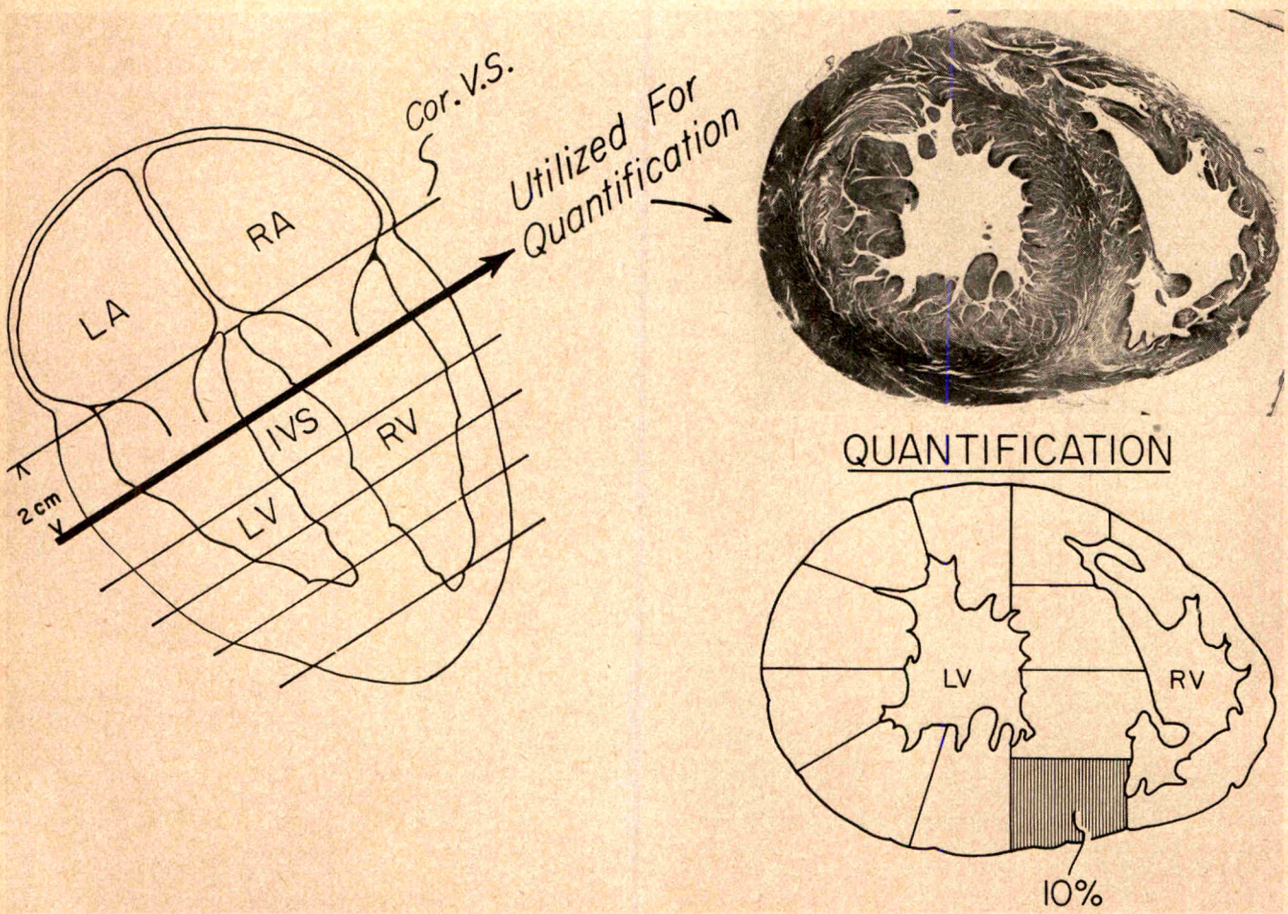


FIGURE 1. Diagram **(left)** depicts the method of examination of the heart. The ventricles were sliced parallel to the coronary sinus (Cor. V. S.). Each slice was 1 cm thick. At least two giant histologic sections **(upper right field of diagram)** of each slice were performed and the one obtained from a site 2 cm caudal to the atrioventricular ring was utilized for quantifying muscle fiber disarray. The left ventricle was divided into 10 equal segments and the amount of myocardial fiber disarray expressed in percent **(lower right** portion of diagram). IVS = interventricular septum; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

related to the normal deviation of the course of normal major muscle bundles.[16–18] Degrees of deviation ranging from orderliness to disorderliness were identified.

The differences in location, distribution and quantitation of myocardial fiber disarray in the single case of idiopathic hypertrophic cardiomyopathy were assessed and compared with findings in the 53 study hearts. Because others[4,7,11] have indicated that the myocardial fiber disarray in idiopathic hypertrophic cardiomyopathy characteristically occurs in the mid portion of the ventricular septum or the free wall of the left ventricle, or both, in this study the giant histologic section 2 cm caudal to the mitral anulus was considered the most informative. The left ventricle in this section was divided into 10 equal segments and the presence of myocardial fiber disarray estimated in percent. For example, if one such segment was totally occupied by myocardial fiber disarray and the other nine had none, the estimate of myocardial fiber disarray was 10 percent (see diagram, Fig. 1). Exact measurement was not possible because the myocardial fiber disarray was frequently haphazardly distributed and its foci varied in size.

The amount of myocardial fiber disarray was considered *minimal* when an occasional focus was present, *mild* if less than 5 percent of the giant section was involved by myocardial fiber disarray, *moderate* when 6 to 20 percent was involved and *marked* when more than 20 percent was involved.

Results

Three types of muscle fiber deviation were seen: a y-shaped (type I), a fascicular (type II) and a more disorganized (type III) arrangement (diagrams, Fig. 2 and 3). Transitions among and combinations of these types existed in each group of hearts. These transitions and combinations were frequently so closely intermin-

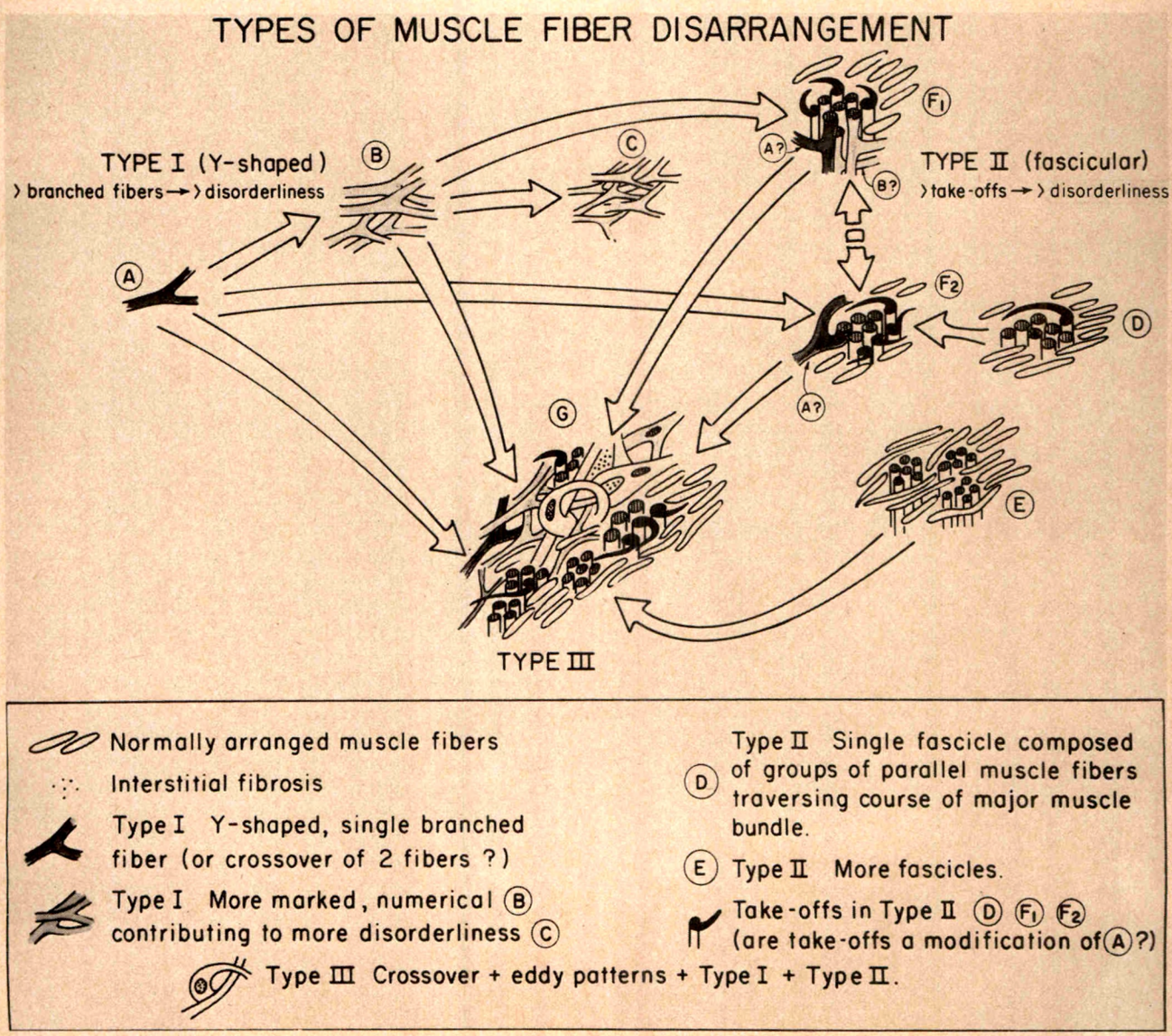
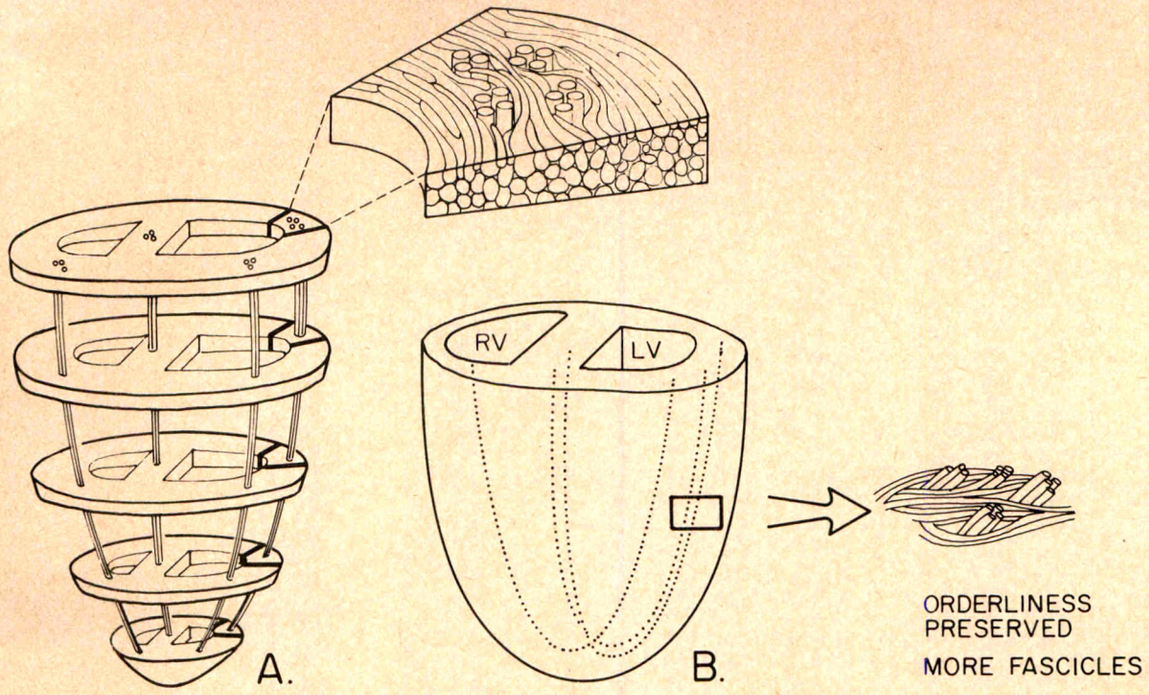


FIGURE 2. Diagram depicting the three types of muscle fiber disarray. Disorderliness is contributed to by a numerical increase in y-shaped fibers (type I [**A, B** and **C**]) and fascicles (type II [**D** and **E**]). In addition, the numerical increase of takeoffs within each fascicle also contributes to disorderliness (F_1 and F_2).



RECONSTRUCTION OF COURSE OF MUSCLE FIBERS IN GIANT HISTOLOGIC SECTIONS AND IN TRANSVERSE SLICES OF THE CARDIAC VENTRICLES.

A. Fascicles, when found in a particular area of a heart, could consistently be traced in all its giant histologic sections.

B. Dotted lines represent the course of one or more fascicles.

FIGURE 3. Reconstruction of course of muscle fibers in all giant histologic sections from all slices of the cardiac ventricles. To the right of diagram **B** is a reconstruction of the interwoven pattern formed by the fascicles and major muscle bundles in the outlined area of the left ventricular wall. LV = left ventricle; RV = right ventricle.

gled within foci of myocardial fiber disarray that it was virtually impossible to measure the quantity of each type individually although types I and II did occur separately in some foci.

Type I: In this type of disarray, the muscle fibers appeared to be arrayed in y-shaped patterns. It is not known whether these patterns were caused by spreading of branches of single muscle fibers or merely by angle formation between two separate muscle fibers, or both. This type I deviation (Fig. 4), whether mild or moderate in quantity, could be seen anywhere in the ventricle whether the segment analyzed was from the septum or the free wall. The pattern also assumed disorderliness. The degree of disorderliness was essentially related to the frequency with which neighboring fibers showed the y-shaped arrangement and branches of muscle fibers crossed those of neighboring fibers. The architecture then resembled that of type III.

Type II: In this type, fascicles of muscle fibers traversed the major left ventricular muscle bundles, particularly the middle one. Each fascicle consisted of a variable number of muscle fibers, arranged in parallel, that manifested "takeoffs" when located at the outer circumferential margins; that is, a branch of a fiber or an entire fiber from a fascicle changed direction to join the course of fibers that composed one of the normal major muscle bundles (Fig. 5C). It could not be determined whether the takeoffs represent branching or a change of direction of a single muscle fiber. The more frequently such takeoffs occurred within one fascicle and within one plane, the more the architecture resembled the disorganized pattern of type III (Fig. 2, 3 and 5). The "fascicles" were seen most frequently in the apex and posterior or anterior ventricular septum. They were less frequent in the mid portion of the ventricular septum and in the free wall. The 53 hearts showed considerable variation in quantity of the type II muscle fiber arrangement in each location. The architectural arrangement of these fascicles when reviewed in each section and combined in the composite of all giant histologic sections obtained in each heart was reminiscent of an interdigitating or woven pattern (Fig. 3). The orderly and disorderly fascicular patterns are depicted in Fig. 5, A to E.

Type III: The arrangement of muscle fibers in this type was more complex than in the other two types. The

complexity was due to combinations and transitions between type I and type II by greater frequency of branching of a greater number of individual neighboring muscle fibers (type I) and more frequent takeoffs (type II). In addition, eddy patterns were seen. The branching and crossover patterns of type III were frequently indistinguishable from those of type I although there was more disorderliness. Types I and II were intricately intermingled with type III and contributed to the disorderliness (Fig. 2, 3 and 6). This type of muscle fiber arrangement was frequently most pronounced in the posterior ventricular septum at the junction of both ventricles and surrounding the posterior penetrating coronary artery (Fig. 7A). The latter structure did not appear to be a scaffold for this disorganization of muscle fibers because it was not consistently present surrounding the artery (Fig. 7B).

The type III muscle fiber arrangement was seen most frequently in the following sites (listed in decreasing order): at the junction of the right and left ventricles, anywhere in the free wall of either ventricle and in the mid portion of the ventricular septum. Once found at a certain location, the larger foci of myocardial fiber disarray (whether type I or II or III) (histologic field as seen when using 4× objective lens) could frequently be traced down in the giant histologic sections of the other slices of the ventricles of one heart (Fig. 3). There was no clear evidence that myocardial fiber disarray occurred more frequently in any group of hearts except possibly for the hearts with cor pulmonale. Every examined heart contained, to at least a minimal degree (1 percent), all three types of muscle fiber arrangement. Table II clarifies further the correlations between the degree of myocardial fiber disarray and the heart weight in each group studied.

Interstitial fibrosis and hypertrophy: Fibrosis most frequently accompanied type I and type III muscle fiber arrangements, but frequently was absent or was present without any change in normal parallel muscle fiber arrangement. The degrees of interstitial fibrosis were variable not only from case to case or from focus to focus of abnormal muscle fiber arrangement, but also within one focus of myocardial fiber disarray. Similarly, muscular hypertrophy was either present or absent in any of the types of muscle fiber arrangement and the degree of hypertrophy was variable from case to case, from focus to focus within a single case and even within one focus of myocardial fiber disarray. Hypertrophy was

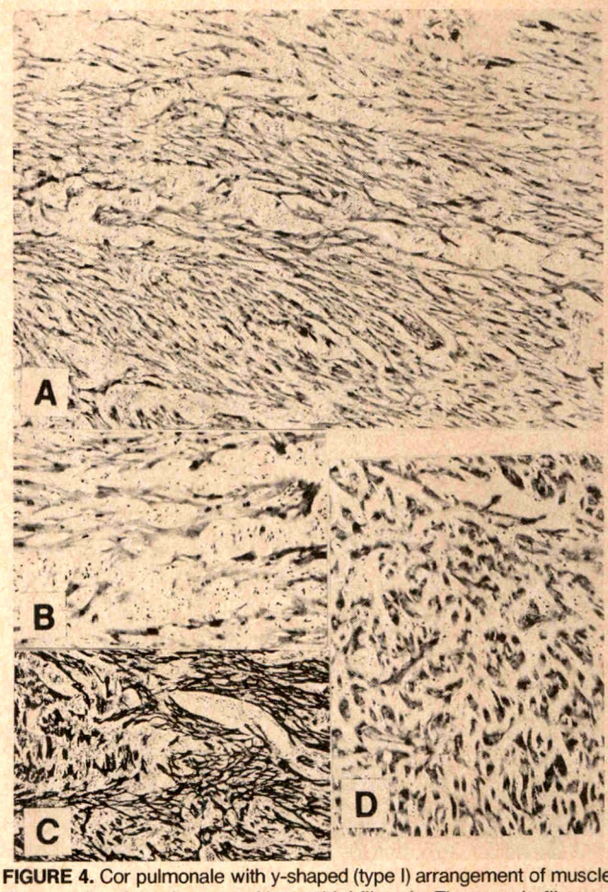


FIGURE 4. Cor pulmonale with y-shaped (type I) arrangement of muscle fibers and various degrees of interstitial fibrosis. The muscle fiber arrangement appears more disorderly in **C** and **D** than in **A** or **B**. Note also that Figure 10B resembles a high power magnification of 4D. (Hematoxylin-eosin stain ×78[**A**], ×62.5[**B**], ×39[**C**] and ×175[**D**]).

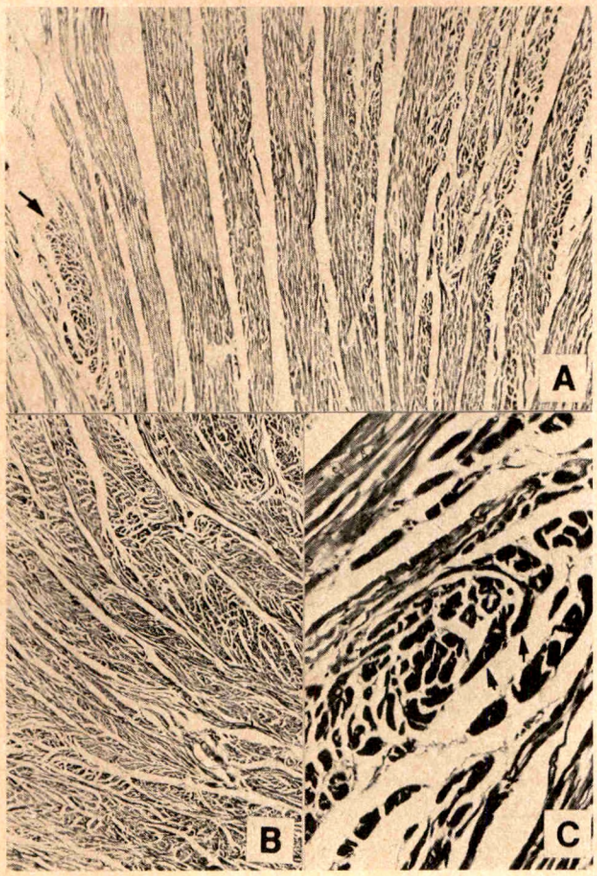
TABLE II

Correlation of Degree of Myocardial Fiber Disarray and Heart Weight in 53 Cases and Control Case of Idiopathic Hypertrophic Cardiomyopathy

	Normal		Systemic Hypertension		ASHD		Cor Pulmonale		Total		IHC	
% MFD	no.	Wt.	no.	Wt.	no.	Wt.	no.	Wt.	no.	Wt.	no.	Wt.
5	11	288	10	433	13	351	1	370	35	360	...	...
6–10	8	288	2	440	2	252	1	500	13	370	...	...
11–20	1	235	...	...	2	247	2	437	5	306	...	...
>20	...	...	...	...	...	...	..	...	...	...	1	800
Total	20	284	12	434	17	327	4	436	53	343	1	800

There is no significant correlation between the degree of myocardial fiber disarray and increase in heart weight, and there is no significantly increased incidence of myocardial fiber disarray in any group of hearts except those with cor pulmonale. In 48 of the 53 hearts there was less than 11 percent myocardial fiber disarray; no heart had more than 20 percent disarray.

ASHD = arteriosclerotic heart disease; IHC = idiopathic hypertrophic cardiomyopathy; MFD = myocardial fiber disarray; no. = number of cases; Wt. = heart weight in grams.



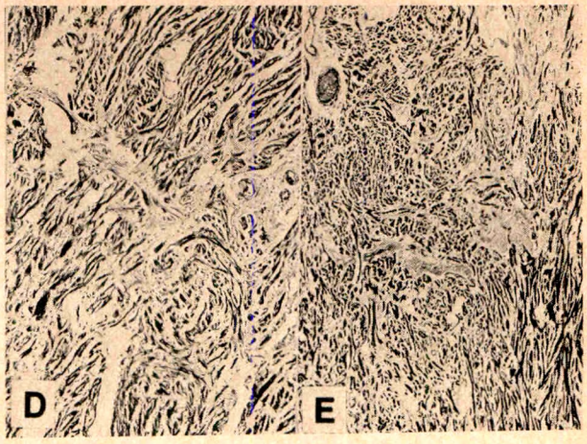


FIGURE 5. Fascicular type (type II) of muscle fiber arrangement **(A)**. **B,** numerical increase of fascicles. **C,** high power magnification of a fascicle with two takeoffs at its right upper margin **(two arrows)**. Takeoffs are more numerous in **D** and **E,** thus contributing to greater disorderliness. **A, B** and **C** are from a heart with arteriosclerotic heart disease, **D** and **E,** from a heart with hypertension. (Hematoxylin-eosin stain, ×74[**A**], ×58.5[**B**], ×586[**C**], ×94[**D**] and ×55[**E**].)



FIGURE 6. Type III muscle fiber arrangement showing eddy and crossover patterns in a heart with cor pulmonale. Note how the y-shaped fibers contribute to muscle fiber disarray. The variation of size of nuclei within these foci is conspicuous. (Hematoxylin-eosin stain ×450[**A**] and ×700[**B**].)

frequently also seen in normally arranged muscle fibers surrounding foci of myocardial fiber disarray. Extreme degrees of hypertrophy (muscle fibers measuring 90 μ in thickness) as described by Van Noorden and Pearse[10] and Olsen[11] were not seen.

Idiopathic hypertrophic cardiomyopathy: All three types of muscle fiber arrangement were seen in the control case of idiopathic hypertrophic cardiomyopathy (Fig. 8 to 10). In this heart, more than 50 percent of the left ventricle was involved by myocardial fiber disarray. The latter, whether type I, II or III, was present in sites where it frequently was seen in the 53 study cases. It was also profusely present in the mid portion of the ventricular septum and in the free wall of the left ventricle, an observation consistent with the findings of others in studies on idiopathic hypertrophic cardiomyopathy. Interstitial fibrosis varied in degree from focus to focus, although it was generally a conspicuous feature. Hypertrophy, although universally present in the heart with idiopathic hypertrophic cardiomyopathy, varied from area to area. It appeared to correspond well with the increased heart weight. The heart of the elderly woman (Fig. 11), with unsuspected asymmetric hypertrophy at autopsy had 20 percent involvement by myocardial fiber disarray. Myocardial fiber disarray does not occur more frequently in acquired disease processes accompanied by cardiac muscle destruction or scarring than in normal hearts. When seen at the border or near an area of scarring, it precedes the insult leading to the destruction of muscle. One can substantiate the evidence by studying all giant sections of such a heart. The sections below or above the area of scarring, or both, will contain myocardial fiber disarray at exactly the same site while the scar is absent. Moreover, the myocardial fiber disarray is located in an anatomic area where it is frequently present irrespective of muscle damage.

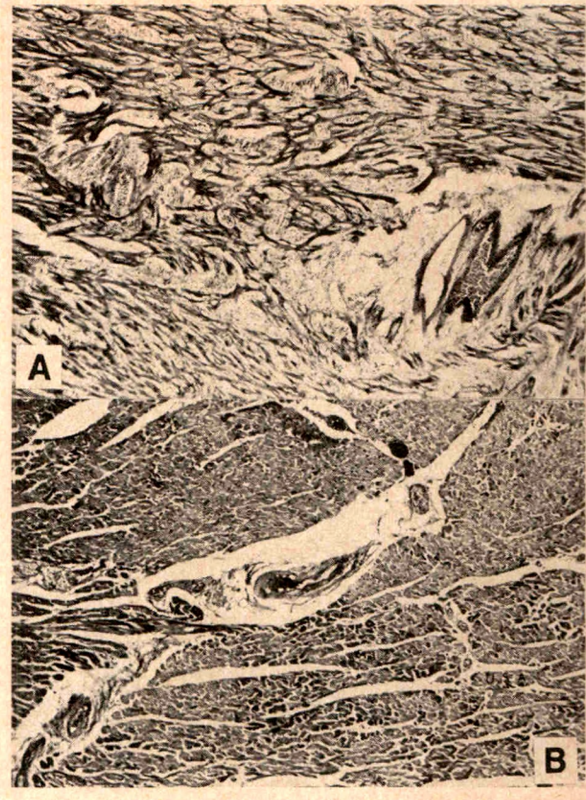
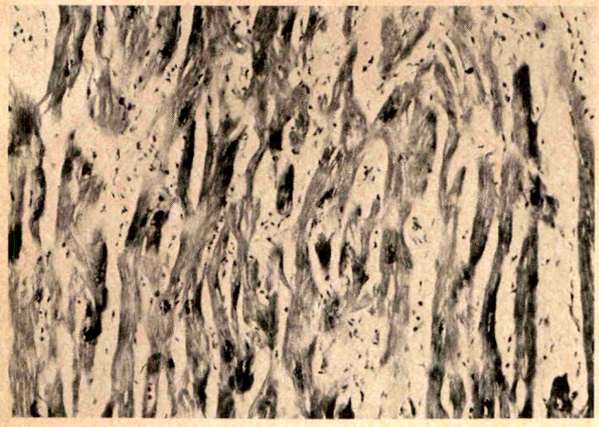


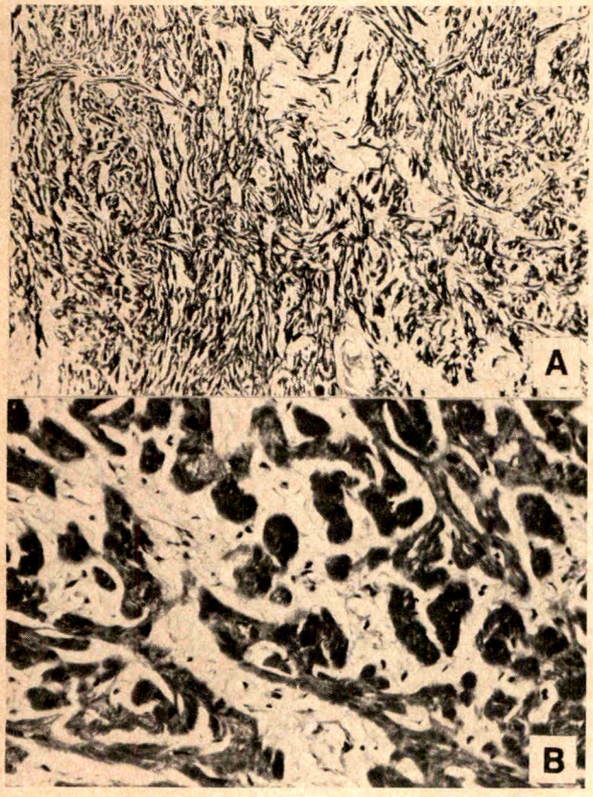
FIGURE 7. Myocardial fiber disarray evident around a penetrating artery **(A)** but absent in the muscle fibers surrounding another penetrating artery **(B)**. (Hematoxylin-eosin stain ×70.)

Comments

Although the ventricular myocardium is generally reported in anatomic studies to consist of rather complex arrangements of muscle bundles, it is typically classified into three muscle layers: the superficial (subepicardial) and the middle and the deep (subendocardial). The intertwining of muscle bundles is apparently not intricate enough to prevent the unfolding of the different ventricular muscle layers.[17,18] The direction of the muscle fibers differs in each of the three layers but, within the confines of each layer, the myocardial fibers are apparently arranged parallel to each other. Textbooks have included fascicles and branching of muscle fibers among the normal histologic features of the myocardium but have not specified the quantity, location or distribution of these features that can be considered entirely normal. Many investigators[1–11] formulated the morphologic features of myocardial fiber disarray. Although the type III arrangement with its eddy, crossover and whorl patterns is usually emphasized, Teare[1] reported that the microscopic findings in all his eight cases were virtually identical, differing only in *degree of cleavage* between coarse muscle bundles. Pare et al.[2] reported muscle fibers forming an interdigitary network of y-shaped (type I) and semicircular bundles (type III). Stampbach and Senn,[19] although aware of Teare's earlier histologic description, did not mention crossover, eddy or whorl patterns in their otherwise characteristic cases of idiopathic hypertrophic cardiomyopathy but did comment on changes similar to those of types I and II. I have described all types of muscle fiber arrangement in this study in the context of studies of other investigators dealing with idiopathic hypertrophic cardiomyopathy or myocardial fiber disarray; there is therefore no doubt that on light microscopy the changes observed in this study are of the same type as those described in earlier studies (Fig. 12).

Hypertrophy: It is not clear whether hypertrophy and particular nuclear changes accompanying its more severe states play an integral role in the definition of myocardial fiber disarray. The variability in degrees of hypertrophy from case to case and from focus to focus within a single case in this study, together with the findings of Van Noorden et al.[4] regarding hypertrophy in classic cases of idiopathic hypertrophic cardiomyopathy with obstruction, suggests that hypertrophy plays a secondary rather than a primary role. This view appears to be further supported by the great variation in heart weight reported in cases of idiopathic hypertrophic cardiomyopathy (350 to 1,250 g[5]). Interstitial





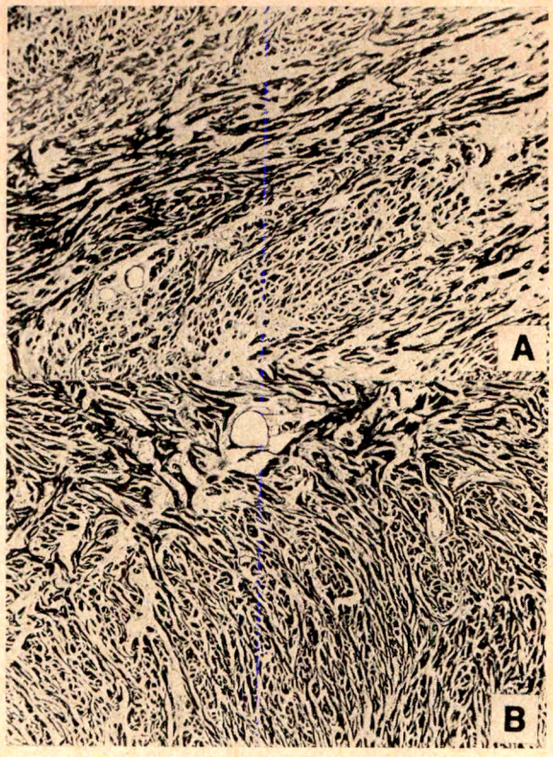


FIGURE 8 (upper left). Y-shaped muscle fiber arrangement with mild interstitial fibrosis in the single heart studied with idiopathic hypertrophic cardiomyopathy. Disorderliness is inconspicuous. (Hematoxylin-eosin stain ×312.5.)

FIGURE 9 (above). Fascicular (type II) muscle fiber arrangement in same case. **B** is more disorderly than **A** in appearance. (Hematoxylin-eosin stain ×70[**A**] and ×112.5[**B**].)

FIGURE 10 (lower left). Type III and transitions between type I, II and III in same case. **B** resembles a high power magnification of Figure 4D. (Hematoxylin-eosin stain ×70[**A**] and ×700[**B**].)

fibrosis similarly appears to play a secondary role and, when present, is not always accompanied by change in direction of muscle fibers.

Differences from hypertrophic cardiomyopathy and implications: The most important differences between the myocardial fiber disarray in our 53 cases and that occurring in idiopathic hypertrophic cardiomyopathy appear to be in location, distribution and quantity. Although Teare[1] in 1958 had already identified the significance of myocardial fiber disarray, the quantitation of myocardial fiber disarray has not yet been sufficiently utilized. The one case of arteriosclerosis with asymmetric configuration reported here (Fig. 11) also indicates the need for a more exact morphologic definition of idiopathic hypertrophic cardiomyopathy. At which (arbitrarily chosen) level of myocardial fiber disarray does one give a heart the morphologic label of idiopathic hypertrophic cardiomyopathy now that it is becoming apparent that secondary heart disease does not necessarily exclude such a diagnosis? Indeed, clinical cases have been reported of coexisting idiopathic hypertrophic cardiomyopathy and atherosclerosis (or hypertension, or both).[20,21] Comparative quantitation of myocardial fiber disarray in such hearts would be important in assessing accurately the clinicopathologic correlations. Further pathologic studies are also needed to correlate pathologic data with clinical findings such as those of Cohen et al.[22] and Mirsky et al.[23] (which

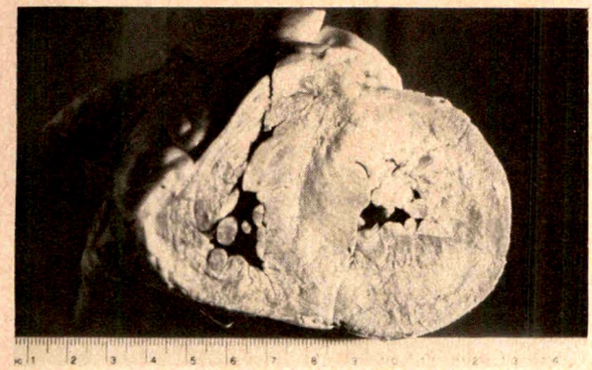


FIGURE 11. View of the base of the heart (440 g) of a 79 year old woman with arteriosclerotic heart disease. The features of asymmetric hypertrophy were an unexpected finding at autopsy. The anterior portion of the ventricular septum measured 2.5 cm in thickness and the posterior left ventricular free wall 1.8 cm. The giant histologic section of the ventricle 2.5 cm caudal to the mitral ring showed less than 20 percent myocardial fiber disarray. The disarray was located in the anterior ventricular septum and in the lateral free wall of the left ventricle, which manifested abnormal thickness.

concern the functional aspect of the ventricular wall). It is not known whether quantitation can play a role in answering the following questions: Why does idiopathic hypertrophic cardiomyopathy manifest itself early in life in certain patients but not until old age in others?[9] Why do some cases of idiopathic hypertrophic cardiomyopathy have a familial background and others do not? Are there significant differences in the quantity of myocardial fiber disarray in such patients? In which respect may systemic hypertension or pulmonary hypertension functionally "challenge" a heart that has a "borderline" (35 to 40 percent) quantity of myocardial fiber disarray located anywhere in the left ventricle? Which quantity, location and distribution of myocardial fiber disarray can be considered entirely normal or not detrimental to the normal function of the heart?

This study also indicates that the posterior and anterior ventricular septum, the apex and the right ventricular free wall should be avoided when performing endomyocardial biopsy to establish a morphologic diagnosis of idiopathic hypertrophic cardiomyopathy. It would be of interest to know how such avoidance would affect the diagnostic accuracy of this procedure.[24]



FIGURE 12. The muscle fiber disarray is similar in the single heart with idiopathic hypertrophic cardiomyopathy **(A)** and in 1 of the 53 study hearts **(B)**. The only difference between **A** and **B** is in degree of muscle fiber hypertrophy. The heart with idiopathic hypertrophic cardiomyopathy weighed 800 g whereas the greatest heart weight in the 53 study cases was 530 g. (Hematoxylin-eosin stain ×112.5.)

Our data are consistent with those of others[4–11] who described the occurrence of myocardial fiber disarray in hearts without idiopathic hypertrophic cardiomyopathy. The major differences in the functional impact that myocardial fiber disarray may have upon the heart appear to be related to the localization, distribution and quantity of myocardial fiber disarray.

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Effect of Heparin-Induced Free Fatty Acid Elevation on Myocardial Oxygen Consumption in Man

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To determine whether acute elevation of plasma free fatty acids influences myocardial oxygen consumption in man, 17 patients underwent a metabolic study consisting of serial measurements of coronary sinus blood flow, heart rate and aortic blood pressure and arterial and coronary sinus determinations of oxygen, carbon dioxide, glycerol and free fatty acids both before and for 30 minutes after the intravenous administration of a bolus dose of 5,000 units of heparin. Of the 17 patients, 9 (group A) were fasting, and 8 (group B) ingested 100 g of fat 3 hours before the study in order to enhance post-heparin lipolysis.

Marked elevation of arterial free fatty acid levels was seen in each group 30 minutes after administration of heparin (group A 713 ± 21 [mean ± standard error of the mean] to 1,757 ± 139 μmoles/liter, $P < 0.001$; group B 721 ± 57 to 2,668 ± 332 μmoles/liter, $P < 0.001$); significant increase in arterial-coronary sinus free fatty acid difference was also noted (group A 139 ± 11 to 298 ± 19 μmoles/liter, $P < 0.001$; group B 147 ± 11 to 334 ± 35 μmoles/liter, $P < 0.001$). Hemodynamic variables, including mean aortic pressure, heart rate, coronary sinus blood flow and coronary vascular resistance, were unchanged. Despite the marked increase in free fatty acids, myocardial oxygen consumption was unchanged 30 minutes after administration of heparin in both groups A and B. Myocardial triglyceride formation after heparin in both groups was suggested by (1) lack of change in cardiac respiratory quotient, (2) net myocardial glycerol uptake after heparin but not in the control state, and (3) oxygen extraction ratios totaling considerably in excess of 100 percent after heparin.

The data suggest that acute elevation of plasma free fatty acids to pathophysiologic levels after heparin-induced lipolysis has no measurable effect on myocardial oxygen consumption in patients in stable condition, probably because the excess free fatty acids are stored as triglycerides rather than oxidized.

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Classic determinants of myocardial oxygen consumption include heart rate, ventricular wall stress and contractile state.[1] However, recent investigators have proposed that when plasma free fatty acid levels are elevated, oxygen demands may increase by mechanisms totally independent of these classic variables. Challoner and Steinberg[2] showed that oxygen consumption of the isolated perfused nonworking rat heart was increased by high concentrations of the free fatty acids palmitate and octanoate in the perfusion medium. Mjøs[3] subsequently showed that myocardial oxygen consumption in the in situ dog heart rose an average of 26 percent when myocardial uptake of free fatty acids was enhanced by infusion of a fat emulsion and heparin.

If these experimental observations have relevance to clinical cardiology, it can be postulated that the elevated levels of plasma free fatty acids commonly seen after myocardial infarction[4–9] may produce additional detrimental metabolic demands on the already oxygen-deficient

myocardium. Furthermore, heparin, a pharmacologic agent often advocated for use in acute myocardial infarction,[10,11] could produce paradoxically detrimental effects through its tendency to elevate free fatty acids by activation of lipoprotein lipase.[12,13]

The purpose of this investigation was to determine whether heparin-induced elevations of plasma free fatty acids might alter myocardial oxygen consumption in patients with stable coronary artery disease under equilibrium conditions.

Material and Methods

Patient Population

After giving informed consent, 17 patients, 15 men and 2 women with a clinical history suggestive of ischemic heart disease, underwent diagnostic cardiac catheterization (Table I). Measurements of cholesterol,[14] triglycerides[15] and serum albumin[16] were made with standard techniques. Serum albumin was 4.2 ± 0.1 g/100 ml (mean ± standard error of the mean). Patients 1 to 9 (group A) fasted for 12 hours before cardiac catheterization; Patients 10 to 17 (group B) fasted for 9 hours, then received orally 270 cc of heavy whipping cream (100 g fat, 9 g carbohydrate, 5.4 g protein) approximately 3 hours before catheterization in order to enhance post-heparin lipolysis. Serum triglycerides in group B averaged 692 ± 374 mg/100 ml upon commencement of cardiac catheterization. No premedication was administered before catheterization.

After completion of the metabolic protocol to be described, all patients underwent selective coronary angiography and biplane left ventriculography. Angiographic data (Table I) revealed that 13 of the 17 patients had significant coronary artery disease. Quantitative angiographic measurements (Table I) were determined as previously described.[17]

TABLE I

Clinical and Angiographic Data

Case no.	Age (yr) & Sex	Chol	TG	GTT	CAD	EF
		Group A (Fasting) (no. = 9)				
1	54F	201	408	−	3V	0.41
2	44M	218	212	−	None	0.48
3	51M	178	185	−	None	0.43
4	24M	136	91	+	2V	0.31
5	59M	163	138	−	2V	0.34
6	36M	179	127	−	2V	0.46
7	49F	225	572	+	1V	0.60
8	67M	208	91	−	3V	0.50
9	40M	178	263	−	None	0.50
		Group B (Lipid-fed) (no. = 8)				
10	48M	201	86	−	1V	0.45
11	52M	163	145	−	2V	0.44
12	38M	235	321	−	3V*	0.66
13	60M	200	317	+	3V	0.40
14	47M	196	200	−	3V	0.27
15	45M	261	390	−	1V	0.46
16	40M	133	164	−	2V	0.58
17	51M	183	172	−	None	0.60

* Patent bypass grafts to all three diseased vessels.
CAD = coronary artery disease, listed as number of vessels (V) diseased with 70 percent or greater stenosis of luminal diameter; Chol = cholesterol (mg/100 ml); EF = left ventricular ejection fraction; GTT = results of 3 hour oral glucose tolerance test; TG = fasting serum triglyceride (mg/100 ml); + = positive; − = negative.

Metabolic Protocol

All patients remained pain-free and in a state of stable equilibrium throughout the study. A small polyethylene catheter was inserted percutaneously into the right brachial artery using the Seldinger technique and advanced to the central aorta. A left antecubital vein was isolated, and a specially designed no. 7 or 8F catheter (Wilton Webster Manufacturing Company, Altadena, California, model CCS-7U-90A or CCS-8U-90B) was positioned in the coronary sinus for sampling of coronary sinus metabolites and measurement of coronary sinus blood flow. The catheter position within the coronary sinus was verified with oximetry. The position of the catheter in relation to skeletal landmarks and to other catheters was noted, and great care was taken to maintain the stability of catheter position throughout the study. The patency of each of the catheters was maintained with 0.9 molar sodium chloride.

After catheter placement, control measurements were made of aortic pressure, heart rate, coronary sinus blood flow and arterial-coronary sinus oxygen content, carbon dioxide content, glucose, free fatty acids, lactate and glycerol. Heparin, 5,000 units, was then administered as an intravenous bolus dose, and the baseline measurements were repeated 10, 20 and 30 minutes after administration of heparin (glycerol was reassayed only at 30 minutes after administration of heparin).

Assay Techniques

Aortic pressure was measured with a Statham P23Gb strain gauge with the reference level 10 cm above table top, and pressure was recorded on a photographic recorder (Electronics for Medicine DR-8).

Coronary sinus blood flow was obtained with a computerized modification of the technique of Ganz et al.,[18] using 0.9 molar sodium chloride at room temperature injected at 36 ml/min. All flow determinations were performed in duplicate, and the reproducibility of repeat determinations was 4.0 percent (mean of differences).

Chemical determinations

1. *Oxygen and carbon dioxide content* were determined with the method of Van Slyke and Neill.[19] In our laboratory, coefficients of variation are less than 0.5 percent for these determinations.
2. *Metablic substrates*
   a. *Glucose and free fatty acids:* Blood was collected in chilled tubes containing sodium ethylene diamine tetraacetic acid (EDTA) to prevent clotting. Blood was assayed for glucose by the glucose oxidase method of Washko and Rice.[20] Free fatty acids were analyzed with the method of Itaya and Ui.[21] Coefficients of variation for the glucose and free fatty acid assays in our laboratory are 1 and 5 percent, respectively.
   b. *Lactate:* Immediately upon withdrawal from the patient, 2 ml of blood was added to 6.5 ml of 6 percent perchloric acid. The tubes were weighed before and after addition of the blood to determine the exact amount added. Tubes were then centrifuged at 6,000 × *g* for 30 minutes to remove the precipitated protein. The perchloric acid extract was titrated to pH 4.5 with 1 molar potassium hydroxide at 0 °C with agitation. Thirty minutes later, precipitated potassium perchlorate was removed from the mixture by centrifugation at 6,000 × *g* for 15 minutes. The supernatant was then assayed for lactate spectrophotometrically by the method of

Hohorst.[22] The coefficient of variation for lactate analysis is 3 percent in our laboratory.

c. *Glycerol:* Glycerol was determined enzymatically using glycerokinase and alpha-glycero-phosphate dehydrogenase according to the method of Wieland.[23]

Calculations

Coronary vascular resistance (CVR) in (mm Hg)/(ml/min):

$$CVR = MAP/CSBF$$

where MAP is mean aortic pressure in mm Hg and CSBF is coronary sinus blood flow (ml/min).

Myocardial respiratory quotient (RQ):

$$RQ = (A\text{-}CS\ CO_2)/(A\text{-}CS\ O_2)$$

where A-CS CO_2 is arterial-coronary sinus carbon dioxide difference (ml/100 ml blood) and A-CS O_2 is arterial-coronary sinus oxygen difference (ml/100 ml blood). Normal RQ values range from 0.70 for pure fat oxidation to 1.00 for pure glucose oxidation. Intermediate values normally suggest combinations of fat and glucose oxidation.[24]

Myocardial oxygen consumption (MVO_2) in ml/min:

$$MVO_2 = (A\text{-}CS\ O_2) \times (CSBF) \times 100$$

This equation for determination of MVO_2 is predicated on the assumption that coronary sinus blood flow is representative of coronary arterial blood flow[18] and that the arterial-coronary sinus difference adequately reflects net myocardial uptake or release of oxygen. Patients with coronary artery disease often have inhomogeneous patterns of regional metabolism and regional blood flow[25] but be-

TABLE II

Hemodynamic and Metabolic Effects of Heparin (5,000 units intravenously) (mean ± standard error of the mean)

	Control State	Minutes After Heparin		
		10	20	30
	Group A (Fasting) (no. = 9)			
Mean aortic pressure (mm Hg)	103 ± 5	105 ± 5	105 ± 4	105 ± 4
Heart rate (min^{-1})	77 ± 5	76 ± 5	76 ± 5	76 ± 6
CSBF (ml/min)	148 ± 9	143 ± 9	144 ± 10	146 ± 10
CVR (mmHg)/(ml/sec)	0.71 ± 0.05	0.75 ± 0.05	0.76 ± 0.06	0.74 ± 0.05
A-CS oxygen (ml/100 ml)	12.4 ± 0.4	12.3 ± 0.4	12.4 ± 0.4	12.2 ± 0.4
MVO_2 (ml/min)	18.1 ± 0.8	17.4 ± 0.7	17.6 ± 0.9	17.6 ± 0.8
Cardiac respiratory quotient	0.75 ± 0.05	0.67 ± 0.05	0.75 ± 0.04	0.71 ± 0.04
Arterial glucose (μmoles/liter)	5322 ± 363	5150 ± 335	5289 ± 344	5178 ± 302
A-CS glucose (μmoles/liter)	261 ± 100	372 ± 89	433 ± 106*	261 ± 100
Arterial lactate (μmoles/liter)	936 ± 74	820 ± 47	844 ± 67	695 ± 45
A-CS lactate (μmoles/liter)	266 ± 31	206 ± 39	218 ± 58	145 ± 38*
Arterial FFA (μmoles/liter)	713 ± 21	2049 ± 285†	2040 ± 263†	1757 ± 139‡
A-CS FFA (μmoles/liter)	139 ± 11	338 ± 53†	320 ± 66*	298 ± 19‡
Arterial glycerol (μmoles/liter)	40 ± 14	. . .	. . .	59 ± 15
A-CS glycerol (μmoles/liter)	−35 ± 16	. . .	. . .	31 ± 12*
Oxygen extraction ratios (%)				
Glucose	28 ± 11	. . .	. . .	40 ± 9
Lactate	14 ± 2	. . .	. . .	8 ± 2†
FFA	33 ± 3	. . .	. . .	72 ± 5‡
Triglyceride	26 ± 13	. . .	. . .	. . .
Total	102 ± 15			120 ± 8
	Group B (Lipid-Fed) (no. = 8)			
Mean aortic pressure (mm Hg)	87 ± 4	86 ± 4	86 ± 4	87 ± 5
Heart rate (min^{-1})	73 ± 3	74 ± 2	74 ± 3	75 ± 2
CSBF (ml/min)	167 ± 25	167 ± 25	163 ± 25	173 ± 23
CVR (mm Hg)/(ml/sec)	0.60 ± 0.08	0.58 ± 0.06	0.61 ± 0.07	0.56 ± 0.06
A-CS oxygen (ml/100 ml)	12.4 ± 0.3	12.2 ± 0.2	11.9 ± 0.2*	11.6 ± 0.3*
MVO_2 (ml/min)	20.5 ± 2.9	20.4 ± 3.0	19.2 ± 2.9	19.8 ± 2.6
Cardiac respiratory quotient	0.72 ± 0.06	0.72 ± 0.05	0.74 ± 0.07	0.74 ± 0.03
Arterial glucose (μmoles/liter)	4500 ± 278	4723 ± 222	4778 ± 222	4945 ± 278†
A-CS glucose (μmoles/liter)	339 ± 78	289 ± 61	311 ± 44	356 ± 67
Arterial lactate (μmoles/liter)	944 ± 90	948 ± 90	1043 ± 134	997 ± 112
A-CS lactate (μmoles/liter)	173 ± 31	172 ± 40	196 ± 37	154 ± 37
Arterial FFA (μmoles/liter)	721 ± 57	2686 ± 294‡	2754 ± 357‡	2668 ± 332‡
A-CS FFA (μmoles/liter)	147 ± 11	361 ± 55†	296 ± 49†	334 ± 35‡
Arterial glycerol (μmoles/liter)	149 ± 23	. . .	. . .	197 ± 34
A-CS glycerol (μmoles/liter)	−46 ± 15	. . .	. . .	19 ± 14‡
Oxygen extraction ratios (%)				
Glucose	37 ± 8	. . .	. . .	41 ± 8
Lactate	11 ± 2	. . .	. . .	9 ± 2
FFA	36 ± 3	. . .	. . .	87 ± 9‡
Triglyceride	33 ± 11	. . .	. . .	. . .
Total	122 ± 13			138 ± 17

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ (compared with control).

A-CS = arterial coronary sinus difference; CSBF = coronary sinus blood flow; CVR = coronary vascular resistance; FFA = free fatty acids; MVO_2 = myocardial oxygen consumption; . . . = not measured.

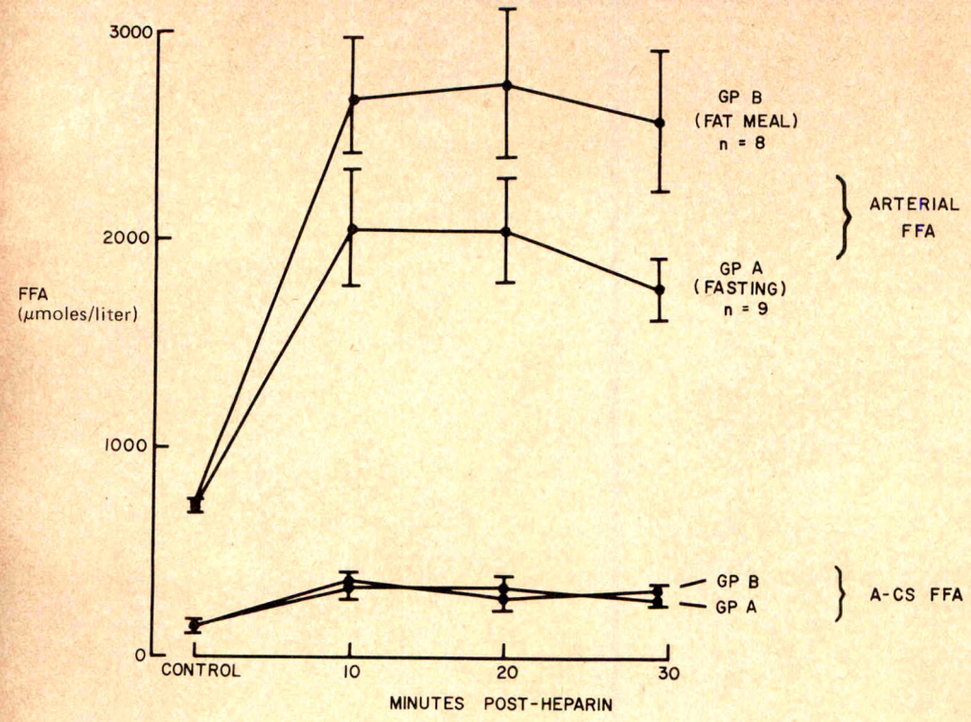


FIGURE 1. Free fatty acids (FFA) (μmoles/liter) after administration of heparin. Groups A and B had similar free fatty acid levels in the control state, but arterial free fatty acids increased significantly ($P < 0.05$) in group B patients after infusion of heparin. Arterial-coronary sinus difference (A-CS) for free fatty acids was similar in both groups throughout the study. GP = group; n = number of patients.

cause each patient in this study served as his own control, we believe that valid comparisons can be made between the control state and the state after the intervention (administration of heparin).

Oxygen extraction ratio (OER) of a given myocardial substrate was defined as that percent of the total myocardial oxygen consumption that could be accounted for if that substrate were completely oxidized. The formula was as follows:

$$\text{OER (\%)} = \frac{(\text{A-CS-S})(\text{O}_2\text{Eq-S})}{(\text{A-CS O}_2)} \times 100$$

where A-CS-S is arterial-coronary sinus difference for a given substrate, A-CS-O_2 is arterial-coronary sinus difference for oxygen and O_2 Eq-S is oxygen equivalent for substrate S (triglyceride 73.5, FFA 24.5, glucose 6, lactate 3). In these calculations, myocardial triglyceride utilization was estimated from arterial-coronary sinus glycerol determinations, assuming that, when coronary sinus glycerol exceeded arterial glycerol, one mole of arterial-coronary sinus glycerol was released per mole of triglyceride oxidized.

Statistics: Data are reported as mean ± standard error of the mean. The paired and nonpaired *t* tests were used to assess differences between paired and nonpaired data respectively.

Results

Because all patients remained in a state of stable equilibrium throughout the study, without evidence of chest pain or lactate production, data from the patients with coronary artery disease and from patients with normal coronary anatomy were analyzed together. Hemodynamic and metabolic changes after the infusion of heparin are shown in Table II.

Hemodynamic data: Mean aortic pressure, heart rate, coronary sinus blood flow and coronary vascular resistance were unchanged after infusion of heparin in both groups.

Free fatty acids: Marked elevation of arterial free fatty acids levels and a significant increase in arterial-coronary sinus free fatty acid difference occurred in both group A (fasting) and group B (fat meal) subjects after infusion of heparin (Fig. 1). As expected, although control arterial and arterial-coronary sinus free fatty acid levels were similar in groups A and B, these levels were higher ($P < 0.05$) 30 minutes after infusion in group B subjects, who had ingested the fat meal before the study; however, the magnitude of myocardial arterial-coronary sinus free fatty acid differences for groups A and B was similar after heparin.

Glucose and lactate: Alterations in glucose and lactate metabolism 30 minutes after heparin were not marked (Table II). Mean myocardial arterial-coronary sinus difference for glucose increased slightly in each group despite the increased free fatty acid availability. Mean myocardial lactate arterial-coronary sinus difference decreased in each group.

Respiratory quotient: This remained essentially unchanged throughout the study and was consistent with the oxidation of fat as the primary myocardial fuel source. Lack of change in respiratory quotient despite an increase in arterial-coronary sinus free fatty acid difference suggested that free fatty acids were stored within the myocardium as triglycerides, rather than oxidized.

Myocardial oxygen consumption: This did not change significantly after heparin in either group de-

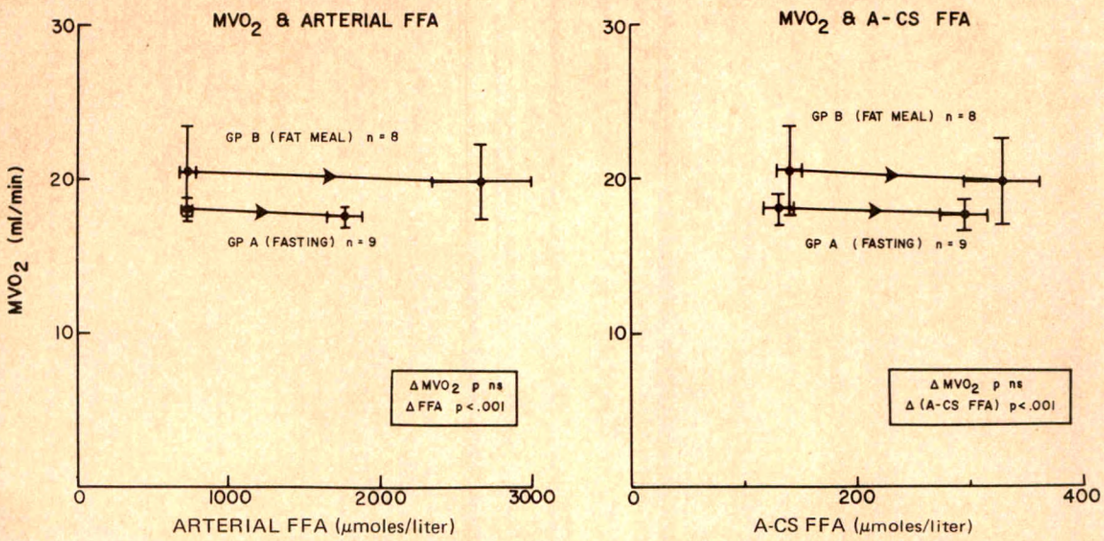


FIGURE 2. Effect of heparin-induced free fatty acid (FFA) elevation on myocardial oxygen consumption (MVO_2). Despite the marked increase in arterial and arterial-coronary sinus (A-CS) free fatty acids in both groups A and B, there was no significant change in myocardial oxygen consumption 30 minutes after administration of heparin. Free fatty acid values are expressed in μmoles/liter. GP = group; n = number of patients; ns = not significant; p = probability.

spite the marked elevations of arterial free fatty acids and significant elevations of myocardial arterial-coronary sinus free fatty acid difference (Fig. 2).

Glycerol: Arterial glycerol was greater in the group B patients both in the control state and after heparin ($P < 0.005$). Arterial glycerol increased slightly, but not significantly, in both groups after heparin. Arterial-coronary sinus difference for glycerol was negative (reflecting net myocardial glycerol release) in the control state in both groups but became positive (reflecting net glycerol uptake) 30 minutes after infusion of heparin. These data are consistent with myocardial triglyceride oxidation in the control state and myocardial triglyceride formation (or storage) 30 minutes after heparin.

Oxygen extraction ratios: These were interpreted cautiously because of rather large variability in data but generally suggested a preponderance of lipid (free fatty acid plus triglyceride) oxidation in the control state, shifting to even more pronounced free fatty acid oxidation 30 minutes after infusion of heparin. Oxygen extraction ratios exceeding 100 percent in the control state in group B and 30 minutes after heparin in both groups probably reflected nonoxidative fates for a portion of the substrates utilized (for example, myocardial triglyceride formation rather than free fatty acid oxidation, or myocardial glycogen formation rather than glucose oxidation).

Discussion

This study has examined the potential interrelation between elevated levels of free fatty acids and myocardial oxygen consumption in patients in stable condition. It provides evidence that, under the experimental conditions cited, increased plasma free fatty acid levels do not cause an increase in myocardial oxygen consumption, but rather result in an increase in myocardial free fatty acid storage as triglyceride.

Methodology: The method used for free fatty acid elevation and the magnitude of the free fatty acid levels achieved were somewhat more physiologic than those of many prior animal experiments relating free fatty acid levels and myocardial oxygen consumption. In our study, the fat meal and infusion of heparin produced free fatty acid levels simulating those found in common stress situations experienced by the patient with ischemic heart disease, namely, unstable angina and acute myocardial infarction.

Although no measurements of myocardial performance were included, we have previously reported that similar heparin-induced elevations of free fatty acids have no effect on myocardial contractility as determined by catheter-tip manometry assessment of left ventricular end-diastolic pressure, maximal rate of rise of left ventricular pressure (dP/dt) and maximal velocity of contractile element shortening (Vmax).[26]

Free fatty acids and myocardial oxygen consumption: Many workers have investigated the concept that free fatty acid elevation might alter myocardial oxygen consumption, and conflicting results have been obtained (Table III). Lack of agreement among the various studies may perhaps be explainable by species specificity, chain-length of free fatty acids used and other differences in experimental methodology.

For several reasons, much of the animal data shown in Table III is of questionable relevance to human myocardial metabolism. Assuming a normal human serum albumin concentration of 4 g/100 ml (0.6 millimolar) and a normal serum free fatty acid concentration of 0.4 to 0.7 millimolar,[34] the free fatty acid/albumin molar ratio in humans is usually 1.0 or less, rising to

TABLE III

Summary of Studies Evaluating Change in Free Fatty Acids and Myocardial Oxygen Consumption

Study	Species	Preparation	Method of Changing FFA	Maximal FFA/Albumin Ratio	ΔFFA	ΔMVO_2
Challoner & Steinberg[2,27] (1966)	Rat	Isolated nonworking perfused heart	Infusion of palmitate & octanoate	9:1	↑	↑
Henderson et al.[28] (1970)	Rat	Isolated working perfused heart	Infusion of linoleate	6:1	↑	↓
Opie[29] (1973)	Rat	Isolated nonworking perfused heart	1. Infusion of linoleate	7:1	↑	0
			2. Infusion of octanoate	∞	↓	↑
		Isolated working perfused heart	Infusion of linoleate	7:1	↑	0
Gmeiner et al.[30] (1975)	Rat	Isolated working perfused heart	Infusion of palmitate	5:1	↑	0
Mjøs[3] (1971)	Dog	In situ heart	Infusion of fat emulsion and IV heparin	10:1*	↑	↑
Most et al.[31] (1973)	Dog	In situ heart	Infusion of fat emulsion and IV heparin	7:1*	↑	0
Mjøs et al.[32] (1974)	Dog	In situ heart	Infusion of beta-pyridylcarbinol	2:1*	↓	0
Regan et al.[33] (1961)	Man	In situ heart	Fat meal and IV heparin	. . .	NM	↑
Present study	Man	In situ heart	Fat meal and IV heparin	3:1	↑	0

* Assuming plasma albumin concentration of 2 g/100 ml for mongrel dog.
ΔFFA = direction of change in free fatty acids; FFA = free fatty acids; IV = intravenous; ΔMVO_2 = direction of change in myocardial oxygen consumption; NM = not measured; ↑ = increased; ↓ = decreased; 0 = unchanged; ∞ = infinitely high (e.g., albumin zero).

about 3 to 4:1 with free fatty acid elevations in the "pathophysiologic" range, but seldom rising above 5:1.

In the animal studies, on the other hand, free fatty acid/albumin molar ratios of 7 to 10:1 were commonly employed (Table III). Spector et al.,[35] and more recently, Willebrands et al.[36] pointed out that when the free fatty acid/albumin molar ratio exceeds about 6:1, the concentration of "unbound" free fatty acids increases markedly, perhaps leading to deleterious effects on cell membranes and enzymes,[37] uncoupling of oxidative phosphorylation,[38,39] precipitation of myocardial intracellular triglycerides[40] and precipitation of extra- and intracellular fatty acid soaps.

Thus, the unphysiologically high free fatty acid levels in many of the animal experiments, together with normal or subnormal albumin levels, led to free fatty acid/albumin ratios, in many cases, far in excess of the physiologic and pathophysiologic range for man. Most of the studies cited in Table III that did not use excessive free fatty acid/albumin ratios found no increase in oxygen consumption when free fatty acids were elevated.

There is no really satisfactory explanation, mechanistically, why free fatty acid elevation should increase oxygen consumption in fasting man. However, there are several theoretical possibilities: (1) uncoupling of oxidative phosphorylation, (2) reduction in the phosphate/oxygen ratio, and (3) free fatty acid esterification. As noted, uncoupling of oxidative phosphorylation has been observed in vitro[38,39] and has been postulated as the mechanism explaining increased myocardial oxygen consumption in vivo in several of the animal studies.[2,3] Uncoupling of oxidative phosphorylation secondary to excess free fatty acids has not been demonstrated in man and probably does not occur under conditions of normal free fatty acid/albumin molar ratios.

As noted by Opie,[41] there would be a small theoretical increase in myocardial oxygen consumption if the myocardium were suddenly changed from a state of pure glucose utilization to pure fat utilization. Under these circumstances, the phosphate/oxygen ratio would fall from 3.15 to about 2.85, leading to an increase in oxygen demand of about 10 percent to produce identical phosphorylation energy equivalents. However, such was not the design of most of the animal studies presented in Table III, nor of this study, in which the unchanged cardiac respiratory quotient of about 0.7 throughout the study confirmed fat oxidation as the major fuel source. Moreover, in our study, it is probable that, despite the increased free fatty acid uptake after administration of heparin, there was no significant increase in free fatty acid oxidation, but rather storage of the excess free fatty acids as myocardial triglyceride.

Myocardial triglyceride formation: Our study provides several lines of evidence to suggest that much of the free fatty acids utilized by the myocardium after heparin was stored as triglyceride, rather than oxidized. First, increased free fatty acid uptake after heparin was accompanied by no change in the respiratory quotient. A significant increase in lipid oxidation would have been expected to depress significantly the respiratory quotient. Second, in the control state, both groups A and B showed a net myocardial release of glycerol, consistent with myocardial hydrolysis of exogenous or endogenous triglyceride. However, after heparin, as the arterial and arterial-coronary sinus free fatty acid levels increased, there was a net myocardial uptake of glycerol, consistent with myocardial triglyceride formation through esterification of free fatty acids with activated glycerol. Fi-

nally, a nonoxidative fate of free fatty acids (such as esterification) after heparin is suggested by oxygen extraction ratios much in excess of 100 percent 30 minutes after heparin in both groups A and B.

Energy required for free fatty acid esterification by myocardium would probably account for only very small changes in myocardial oxygen consumption if data obtained on free fatty acid esterification in adipose tissue are of relevance.[42] Thus, if increased free fatty acids after heparin were stored as myocardial triglyceride rather than oxidized, no measurable change in myocardial oxygen consumption would necessarily be expected. Human beings may have an increased capacity to form myocardial fat stores since it has been noted that, compared with most animal species, the human heart possesses a greater supply of subepicardial adipose tissue.[43]

Clinical implications: Our study in human beings in stable condition has shown that pathophysiologic elevations of free fatty acids are associated with no change in myocardial oxygen consumption. This finding, despite considerable animal data to the contrary, is not unreasonable as previously explained. Whether these findings in patients in stable condition can be extrapolated to patients with unstable manifestations of ischemic heart disease is not known. Although there are as yet no reports of the effects of increased free fatty acid levels on myocardial oxygen consumption in acute myocardial infarction or angina pectoris, several recent studies are of interest.

Dageneis and Talbert[44] observed that free fatty acid elevations in patients with coronary artery disease had no effect on anginal threshold, S-T segment changes or lactate production during atrial pacing. Their findings therefore suggest that elevated free fatty acid levels are inconsequential in modifying the oxygen requirements of patients with coronary artery disease under conditions of dynamic stress. However, their study, like ours, was by necessity short-term in nature, and the possibility still exists that increased plasma free fatty acids may over time stimulate alterations of myocardial oxygen consumption that are different from those observed during a 30 minute period.

Most et al.[45] recently showed that, in the experimental pig myocardial infarction, S-T segment-mapping estimates of myocardial infarct size were not increased in the presence of elevated free fatty acid levels. Their study suggests that free fatty acid elevations probably are unrelated to myocardial oxygen consumption in the setting of experimental myocardial infarction.

Saliba et al.[46] recently reported that heparin infused in large doses reduced epicardial S-T segment elevation, myocardial creatine kinase depletion and histologic evidence of myocardial necrosis after acute coronary occlusion in the dog. In human beings, they[47] showed that anticoagulant doses of heparin reduced the electrocardiographic pattern of injury. Free fatty acid levels were not reported in these studies, but large doses of heparin did not produce adverse effects under the setting of acute myocardial ischemia.

Although our study and the recent data just cited support the premise that pathophysiologic elevations of free fatty acids may not adversely alter myocardial oxygen consumption in ischemic heart disease, further studies are needed to investigate the other reported detrimental effects of increased free fatty acids (such as increased arrhythmias,[34] decreased contractility[48] and long-chain fatty acid acyl-coenzyme A inhibition of adenine nucleotide translocase,[49] particularly since recent studies have demonstrated that elevated free fatty acid levels associated with acute myocardial infarction can be reduced with several interventions, including administration of nicotinic acid derivatives,[50] high carbohydrate feedings[51] and glucose-insulin-potassium infusions.[52–54]

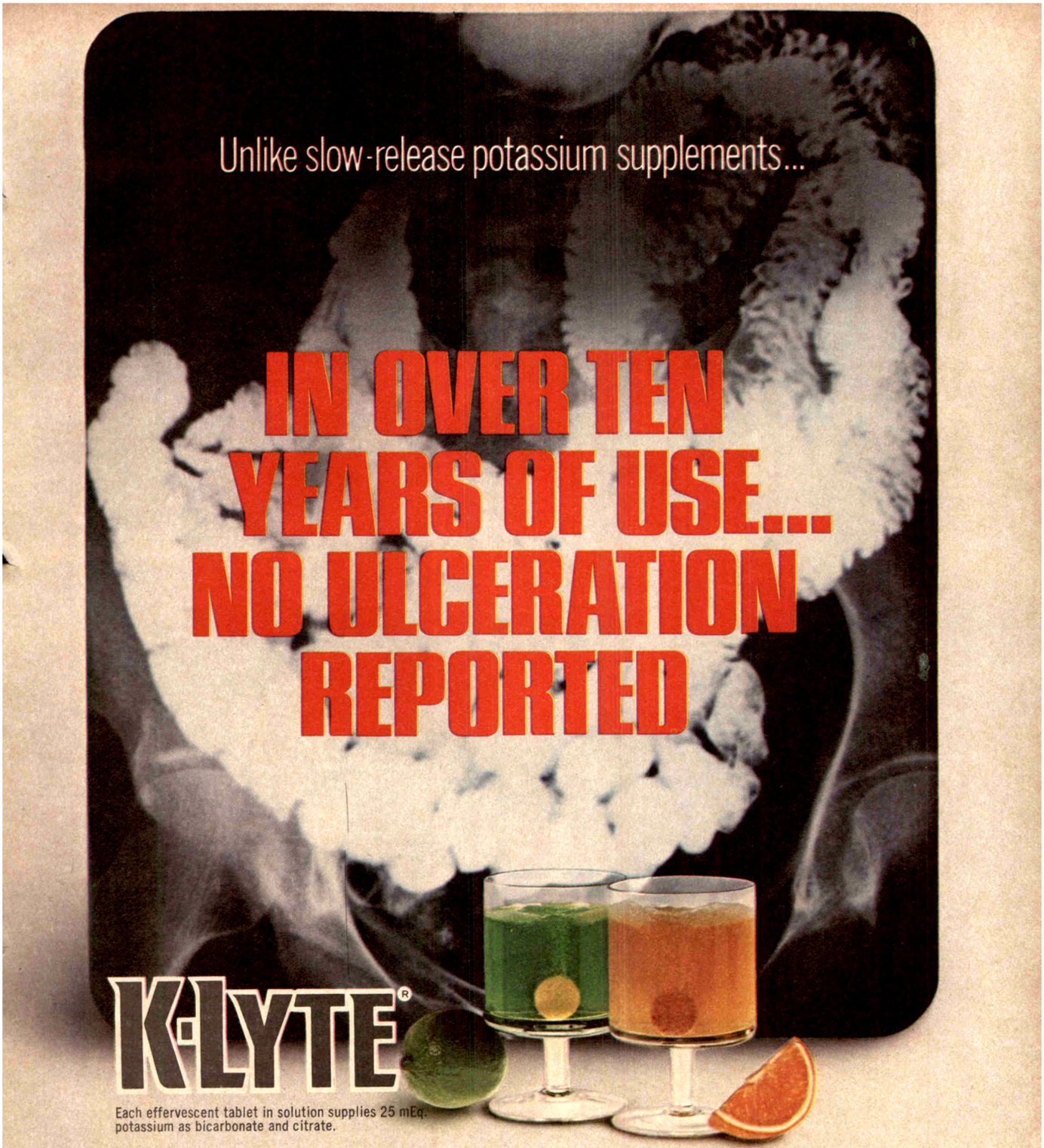
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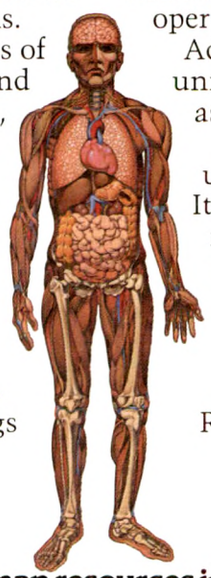
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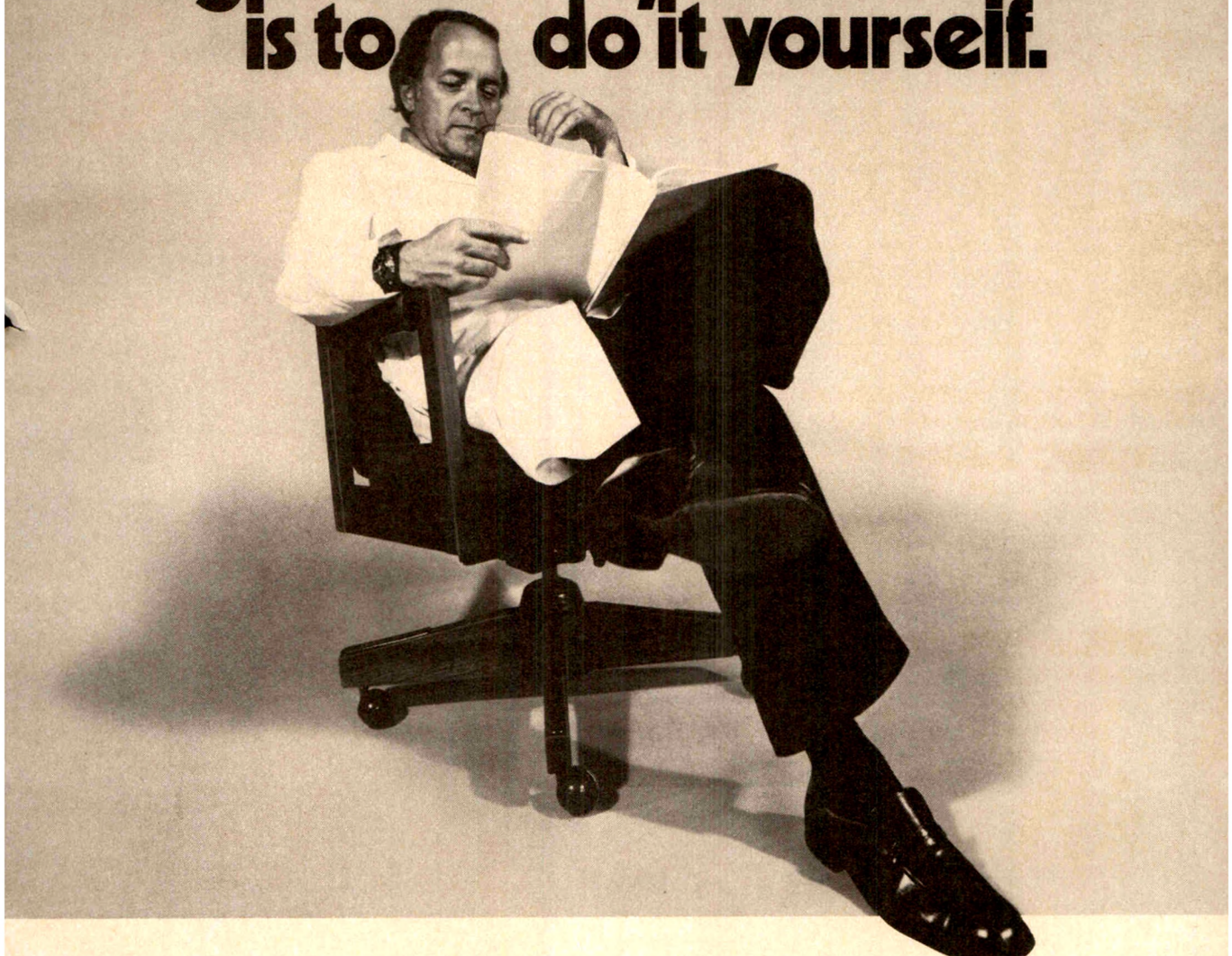


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So, who's the best among the many scanning services? You judge. We at Omnimedical offer 3 programs for reel-to-reel or cassette tapes, each with a maximum turnaround time of 24 hours. There's the free recorder program, the regular scanning service, and the same-day service pick-up program if you're in our area. All feature the most comprehensive report in the business—including a computerized, quantitative analysis, a trend analysis of heart rate and ST segment level, and real-time recordings of abnormalities and symptomatology mounted in booklet form.

Omnimedical

P.O. Box 1277, Paramount, CA 90723 (213) 633-6660
PLEASE SEND DCG SCANNER SERVICE INFORMATION TO:

NAME

ADDRESS

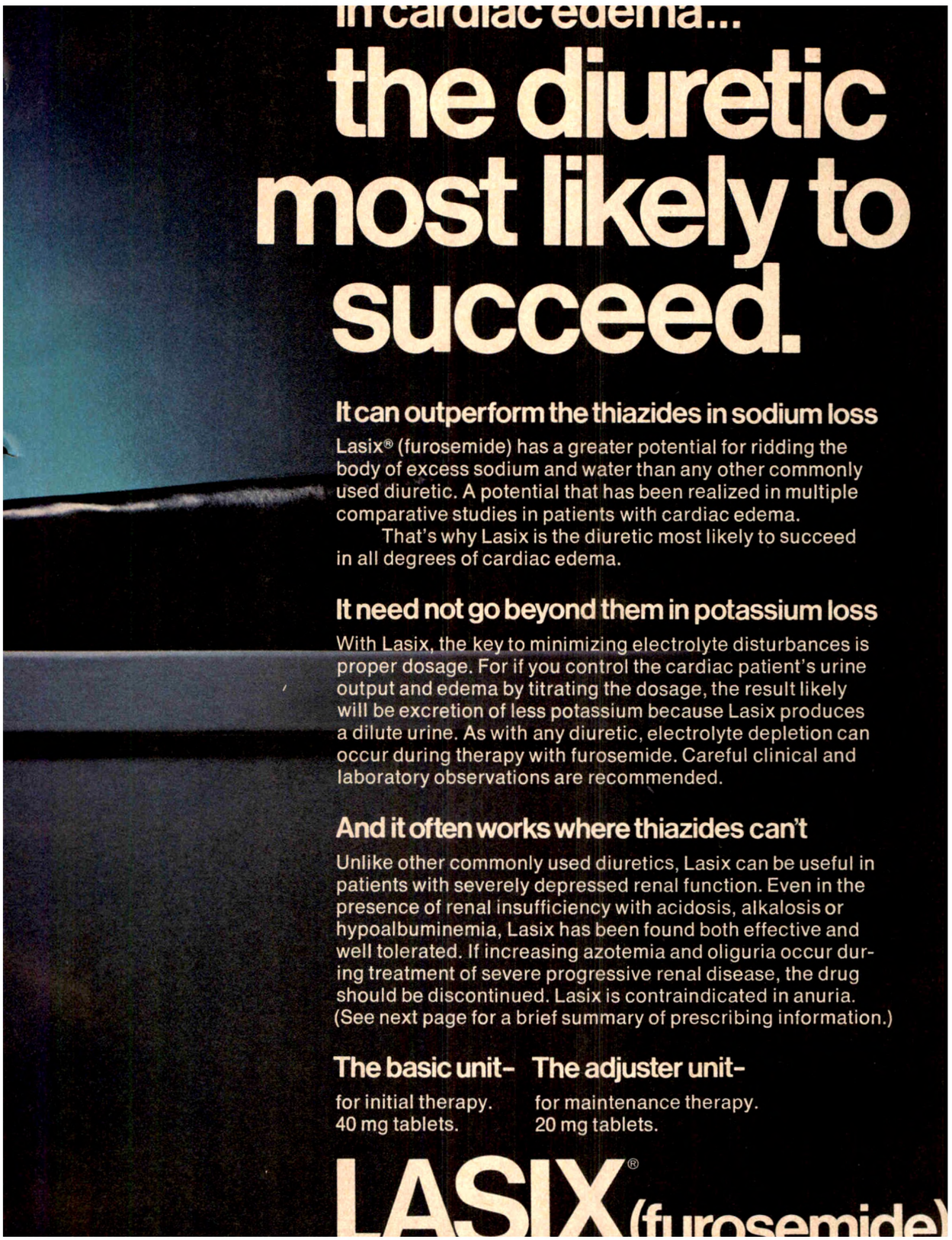
CITY STATE ZIP

PHONE TITLE

ORGANIZATION, HOSPITAL

AJC-9





In cardiac edema...

the diuretic most likely to succeed.

It can outperform the thiazides in sodium loss

Lasix® (furosemide) has a greater potential for ridding the body of excess sodium and water than any other commonly used diuretic. A potential that has been realized in multiple comparative studies in patients with cardiac edema.

That's why Lasix is the diuretic most likely to succeed in all degrees of cardiac edema.

It need not go beyond them in potassium loss

With Lasix, the key to minimizing electrolyte disturbances is proper dosage. For if you control the cardiac patient's urine output and edema by titrating the dosage, the result likely will be excretion of less potassium because Lasix produces a dilute urine. As with any diuretic, electrolyte depletion can occur during therapy with furosemide. Careful clinical and laboratory observations are recommended.

And it often works where thiazides can't

Unlike other commonly used diuretics, Lasix can be useful in patients with severely depressed renal function. Even in the presence of renal insufficiency with acidosis, alkalosis or hypoalbuminemia, Lasix has been found both effective and well tolerated. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. Lasix is contraindicated in anuria.
(See next page for a brief summary of prescribing information.)

The basic unit–
for initial therapy.
40 mg tablets.

The adjuster unit–
for maintenance therapy.
20 mg tablets.

LASIX® (furosemide)



LASIX®
(furosemide)

A brief summary of the Prescribing Information for

Lasix® (furosemide) Tablets 20 mg and 40 mg

WARNING—Lasix (furosemide) is a potent diuretic which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Indications—Lasix (furosemide) is indicated for the treatment of the edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.

Hypertension—Lasix (furosemide) may be used for the treatment of hypertension alone or in combination with other antihypertensive drugs. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controllable with Lasix (furosemide) alone.

CONTRAINDICATIONS—Because animal reproductive studies have shown that Lasix (furosemide) may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. (See "Additional Information.")

Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids.

Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter, and abnormalities corrected or the drug temporarily withdrawn.

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix (furosemide) is best carried out in the hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In those instances where potassium supplementation is required, an oral liquid preparation should be used rather than enteric-coated potassium salts.

There have been several reports, published and unpublished, concerning nonspecific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics.

These small-bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred.

Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occurs.

Patients with known sulfonamide sensitivity may show allergic reactions to Lasix (furosemide).

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion.

Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

When parenteral use of Lasix (furosemide) precedes its oral use, it should be kept in mind that cases of tinnitus and reversible hearing impairment have been reported. There have also been some reports of cases in which irreversible hearing impairment occurred. Usually, ototoxicity has been reported when Lasix (furosemide) was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were often given. If the physician elects to use high dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable (for adults, it has been reported that an infusion rate not exceeding 4 mg Lasix [furosemide] per minute has been used).

Increases in blood glucose, and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Lasix (furosemide) may lower serum calcium levels, and rare cases of tetany have been reported.

Patients receiving high doses of salicylates, in conjunction with Lasix (furosemide) may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, Lasix (furosemide) and cephaloridine should not be administered simultaneously.

Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Various forms of dermatitis, including urticaria and rare forms of exfoliative dermatitis, erythema multiforme, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea.

Anemia, leukopenia, aplastic anemia, and thrombocytopenia (with purpura). Rare cases of agranulocytosis which responded to treatment.

In addition, the following rare adverse reactions have been reported; however, relationship to the drug has not been established with certainty: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, thrombophlebitis and emboli and acute pancreatitis.

Lasix (furosemide)-induced diuresis may be accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, increased perspiration, urinary bladder spasm, and symptoms of urinary frequency.

Dosage and Administration

ADULTS

The usual adult dose of Lasix (furosemide) is 20 to 80 mg given as a single dose.

If the diuretic response with a single dose of 20 to 80 mg is not satisfactory, the following schedule should be used: Increase this dose by increments of 20 or 40 mg not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily. The dose of Lasix (furosemide) may be carefully titrated up to 600 mg per day in those patients with severe clinical edematous states.

With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable.

Hypertension—The usual dose of Lasix (furosemide) is 40 mg twice daily both for initiation of therapy and for maintenance. Careful observations for changes in blood pressure must be made when this compound is used with other antihypertensive drugs, especially during initial therapy. The dosage of other agents must be reduced by at least 50 percent as soon as Lasix (furosemide) is added to the regimen to prevent excessive drop in blood pressure. As the blood pressure falls under the potentiating effect of Lasix (furosemide), a further reduction in dosage, or even discontinuation, of other antihypertensive drugs may be necessary. It is further recommended, if 40 mg twice daily does not lead to a clinically satisfactory response, to add other hypotensive agents, e.g., reserpine, rather than to increase the dose of Lasix (furosemide).

INFANTS AND CHILDREN

Pediatric Administration: The usual initial dose of oral Lasix in infants and children is 2 mg/kg body weight, given as a single dose. If the diuretic response is not satisfactory after the initial dose, dosage may be increased by 1 or 2 mg/kg not sooner than 6 to 8 hours after the previous dose. Doses greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

How Supplied—Lasix Tablets 40 mg (furosemide) supplied as white, round, monogrammed, scored tablets.

Lasix Tablets 20 mg (furosemide) supplied as white, oval, monogrammed tablets.

Note: Dispense in dark containers. Exposure to light may cause slight discoloration which, however, does not alter potency.

Additional Information

Toxicology

The acute toxicity of Lasix (furosemide) has been determined in mice, rats, and dogs. In all three animal species, the oral LD_{50} of Lasix (furosemide) exceeded 1000 mg/kg of body weight, while the intravenous LD_{50} ranged from 300 to 680 mg/kg. Intragastric injection of the drug in newborn rats resulted in an LD_{50} of 380 mg/kg.

The acute toxicity of high doses of Lasix (furosemide) was characterized by convulsions, paralysis, and collapse. Surviving animals often became dehydrated and depleted of electrolytes due to the diuresis induced by Lasix (furosemide). In the newborn rats, intragastric injection of the drug caused hyperactivity and anorexia.

Chronic toxicity studies with Lasix (furosemide) were done in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred, with all doses higher than 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day). A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg (83 percent of the maximal recommended human dose of 600 mg per day).

Reproductive Studies

The effects of Lasix (furosemide) on embryonic and fetal development and on pregnant dams were studied in mice, rats, and rabbits.

Lasix (furosemide) caused unexplained maternal deaths and abortions in the rabbit when 50 mg/kg (4 times the maximal recommended human dose of 600 mg per day) was administered between days 12 to 17 of gestation. In a previous study the lowest dose of only 25 mg/kg (2 times the maximal recommended human dose of 600 mg per day) caused maternal deaths and abortions. In a third study, none of the pregnant rabbits survived a dose of 100 mg/kg. Data from the above studies indicate fetal lethality which can precede maternal deaths.

The results of the mouse study and one of the three rabbit studies also showed an increased incidence of hydronephrosis (distention of the renal pelvis and, in some cases, of the ureters) in fetuses derived from treated dams as compared to the incidence in fetuses from the control group.

HOECHST-ROUSSEL
PHARMACEUTICALS INCORPORATED
SOMERVILLE, NEW JERSEY 08876

REG TM HOECHST AG

Edition 6/77

Q6652J-677


Do you also take a reading
of the other tension...
140
160
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120
100
SPHYGMOMANOMETER
220
80
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Certified
40
280
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300
mmHg

Does the patient fidget? Seem unduly restless, irritable and hypersensitive? Have a tendency to sweat, tire easily, complain of vague and varied aches and pains?

Excessive psychic tension may well be a distressing problem in your hypertensive patient.

If so, Valium (diazepam) can be an invaluable addition to your antihypertensive program. Valium provides a response you know, want and trust. A response that means dependable relief of psychic tension and anxiety and their more distressing symptoms—symptoms that may range from overconcern with bodily "aches" to irritability, hypersensitivity and emotional lability. And Valium works promptly, with initial calming in hours and significant improvement within days.

Equally important: Valium is generally well tolerated and can be used concomitantly with antihypertensive agents, diuretics, cardiac glycosides and most other primary medications. Though drowsiness, ataxia and fatigue are sometimes encountered, these and more serious side effects are rarely a problem.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

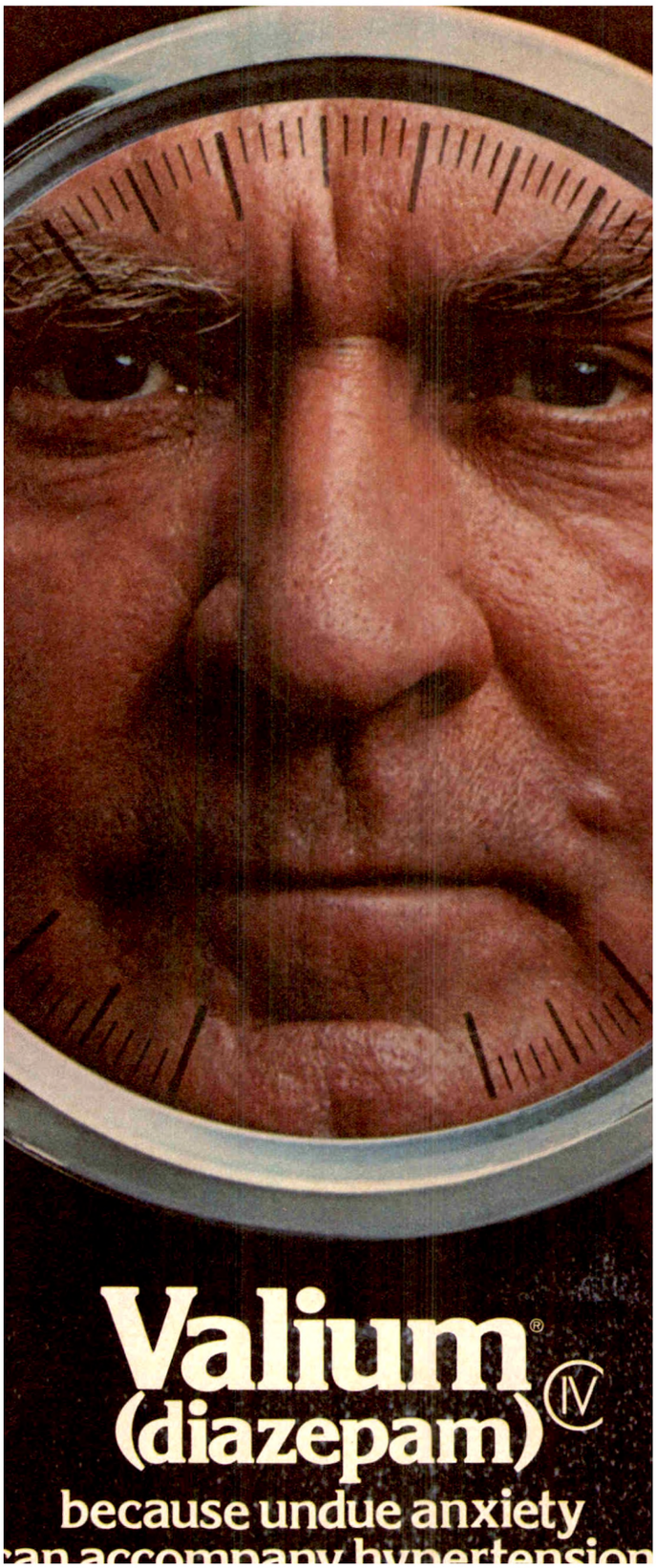
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

Dosage: Individualize for maximum beneficial effect. *Adults:* Tension, anxiety and psychoneurotic states, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).

Supplied: Valium® (diazepam) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110


Valium®
(diazepam)
IV
because undue anxiety

Green light for hepatic function.

Measure liver function using Cardio-Green® (CG®) (Sterile Indocyanine Green, USP) injectable dye: A product that's been established in over 20 years of use.

The plasma disappearance of Cardio-Green shows good correlation with Bromsulphalein® (BSP®)[1] (Sulfobromophthalein Sodium Injection, USP) and *overall is a superior product* for the quantification of hepatic function and blood flow.

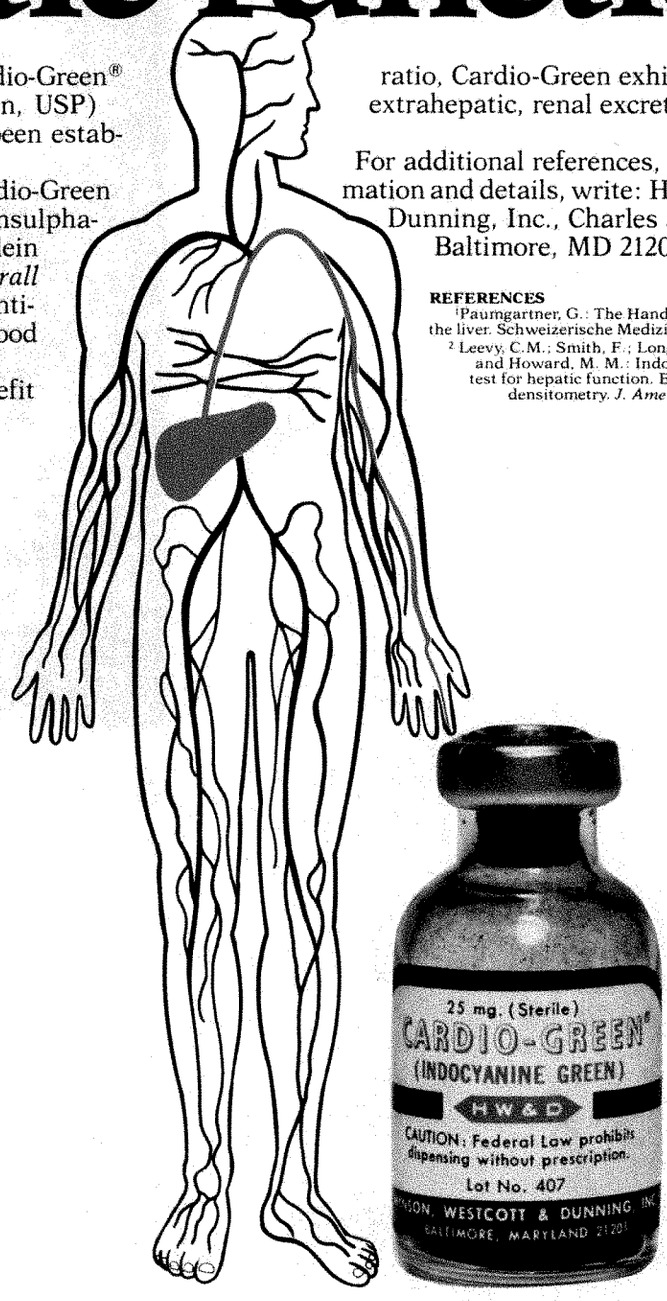
In addition to a superior risk/benefit ratio, Cardio-Green exhibits none of BSP's extrahepatic, renal excretion, and enterohepatic circulation.[2]

For additional references, professional information and details, write: Hynson, Westcott & Dunning, Inc., Charles and Chase Streets, Baltimore, MD 21201. (301) 837-0890.

REFERENCES

[1] Paumgartner, G.: The Handling of Indocyanine Green by the liver. Schweizerische Medizinische Wochenschrift (1975).

[2] Leevy, C.M.; Smith, F.; Longueville, J.; Paumgartner, G.; and Howard, M. M.: Indocyanine Green clearance as a test for hepatic function. Evaluation by dichromatic ear densitometry. *J. Amer. Med. Assn.* 200, 136 (1967).



BEFORE PRESCRIBING, PLEASE CONSULT THE INSERT WHICH ACCOMPANIES THE PRODUCT, A BRIEF SUMMARY FOLLOWS:

DESCRIPTION. Cardio-Green is a sterile, water soluble, tricarbocyanine dye with a peak spectral absorption at 800-810 nanometers in plasma or blood.

ACTION. CG permits recording of indicator-dilution curves for both diagnostic and research purposes independently of fluctuations in oxygen saturation. In the performance of dye dilution curves, a known amount of dye is usually injected as a single bolus as rapidly as possible via a cardiac catheter into selected sites in the vascular system. A recording instrument (oximeter or densitometer) is attached to a needle or catheter for sampling of the dye-blood mixture from a systemic arterial sampling site.

Ear oximetry has also been used and makes it possible to monitor the appearance and disappearance of CG without blood withdrawal.

Following intravenous injection, CG is rapidly bound to plasma protein, of which albumin is the principle carrier. It has a hepatic storage capacity of 70 mg/mg/100 ml and excretory Tm of 7.5 mg/min in healthy subjects. CG undergoes no significant extrahepatic or enterohepatic circulation; simultaneous arterial and venous blood estimations have shown negligible renal, peripheral, lung or cerebrospinal uptake of the dye. CG is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile. After biliary obstruction, the dye appears in the hepatic lymph, independently of the bile, suggesting that the biliary mucosa is sufficiently intact to prevent diffusion of the dye, though allowing diffusion of bilirubin. These characteristics make CG a helpful index of hepatic function.

INDICATIONS. For determining cardiac output, hepatic function and liver blood flow and ophthalmic angiography.

CONTRAINDICATIONS. The safe use of Cardio-Green during pregnancy has not been established.

WARNINGS. CG Powder and Solution: CG is unstable in aqueous solution and must be used within 10 hours. However, the dye is stable in plasma and whole blood so that samples obtained in discontinuous sampling techniques and stored at 2-8° may be read within a 2-day period. Sterile techniques should be used in handling the dye solution as well as in the performance of the dilution curves.

PRECAUTIONS. Probenecid in doses of from 25 to 100 mg/kg has been shown to affect the hepatic uptake, storage and removal of CG in dogs; this has not been reported in humans, but should be considered.

ADVERSE REACTIONS. CG contains a small amount of sodium iodide and should be used with caution in patients who have a history of allergy to iodides. Radioactive iodine uptake studies should not be performed for at least a week following the use of CG.

DOSAGE AND ADMINISTRATION. The usual dosages of CG are as follows: for dilution curves: Adults – 5 mg; Children – 2.5 mg; and Infants – 1.25 mg; for hepatic function, 0.5 mg per kg of body weight.

HEPATIC FUNCTION STUDIES. Due to its absorption spectrum, changing concentrations of Cardio-Green (Sterile Indocyanine Green, USP) in the blood can be monitored by ear densitometry or by obtaining blood specimens for photometric determination using percentage retention of dye from a single, 20-minute sample or using disappearance rate at timed intervals. The technique for both methods is described in the instructions, which accompany the product.

NORMAL VALUES. Percentage disappearance rate in healthy subjects is 18-24% per minute. Normal biological half-time is 2.5-3.0 minutes.

SUPPLIES. A 25 mg vial (NDC 0011-8361-20) and 50 mg vial (NDC 0011-8362-55) and 10 mg (NDC 0011-8363-72) and 40 mg (NDC 0011-8364-54) CG Single Use Unit, with calibrated syringes. All put-ups with aqueous solvent.

Bromsulphalein, BSP, Cardio-Green, CG, Hynson, Westcott & Dunning, Inc. and ◆ are trademarks of Hynson, Westcott & Dunning, Inc.

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

For complete details, please see the full prescribing information.

BOEHRINGER INGELHEIM

Boehringer Ingelheim
Boehringer Ingelheim Ltd., Elmsford, N.Y. 10523

Illustrated: **Queen of Hearts**...from the series "Le jeu de Charles VII" created in Lyons. France in the second decade of the 16th century.

The gentlemen of this series had names; the ladies bore heroic slogans. This pack honored the life of Charles VII (1422-1461).



What's in the cards for the anginal patient?

For centuries, dealing with the heart's ills has been the subtlest of arts, an intricate shuffling of skill and science. Even today, evaluating a drug for chronic angina pectoris involves the art of medicine as well as its science.

During more than a decade of clinical experience, compounding both science and art, Persantine has often been found useful in the long-term management of chronic angina pectoris.* It may:

eliminate or reduce the frequency of anginal attacks

improve exercise tolerance

reduce nitroglycerin requirements

Give enough...long enough (recommended dosage: 50 mg t.i.d. at least one hour before meals for 60 to 90 days or longer).

Persantine®

(dipyridamole) Tablets of 25 mg

non-nitrate
coronary vasodilator

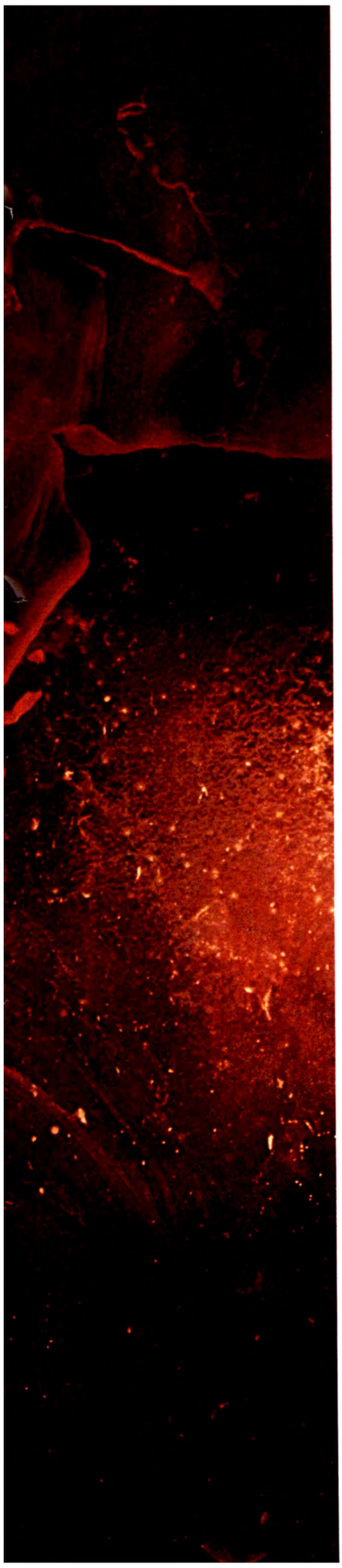


A Broken Heart

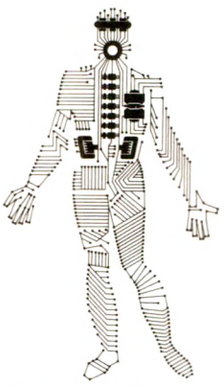
It can start with a little high blood pressure

Infarction with rupture of the wall in the left ventricle of man, 66, with mild hypertension. Blood clot in pericardial sac. Postmortem.

Photographed exclusively for Boehringer Ingelheim by Lennart Nilsson.



Reach for normal blood pressure



In mild to moderate hypertension

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Catapres can make a diuretic look good.

When more than a diuretic is needed, adding Catapres usually lowers blood pressure more.[1]

You can add Catapres to Catapres to get pressure down near normal.

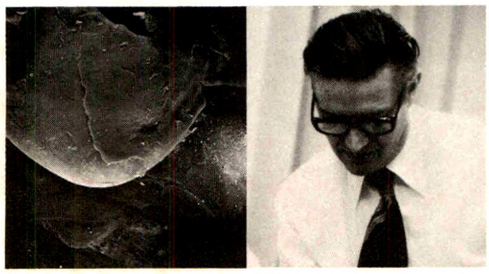
Wide therapeutic dosage range—0.2 mg to 2.4 mg* daily. Catapres may be all you need to reach near-normal levels.

*Doses as high as this have rarely been employed.

Catapres usually doesn't add a lot of problems.

The most common side effects—dry mouth, drowsiness, sedation—generally tend to diminish with time. When stopping Catapres, reduce dosage gradually over two to four days to avoid a possible rapid rise in pressure.

Please see next page of advertisement for a brief summary of the prescribing information including precautions, warnings, and adverse reactions.



Hypertension through the lens of Lennart Nilsson. The photographic genius of Lennart Nilsson has revealed extraordinary details of the human organism. Now, Boehringer Ingelheim has commissioned an exclusive series of photographs by Nilsson depicting hypertensive damage. This series, presented in the interest of continuing medical education, vividly records the progression of an insidious disease.

In mild to moderate hypertension

The Catapres Potential: blood pressure not just down, but down near normal

Catapres® Tablets of 0.1 and 0.2 mg (clonidine HCl)

Start with Catapres when a diuretic is wrong for your patient

Add Catapres when a diuretic alone doesn't let you reach near-normal pressure

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone, and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase: congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100.

For complete details, please see full prescribing information.

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Reference: 1. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim Ltd.
Elmsford, New York 10523

Significance of Subendocardial S-T Segment Elevation Caused by Coronary Stenosis in the Dog

Epicardial S-T Segment Depression, Local Ischemia and Subsequent Necrosis

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A model of partial thickness ischemia has been developed using subendocardial S-T elevation without epicardial S-T elevation to detect partial thickness ischemia which is sufficient to cause subsequent necrosis. Subendocardial blood flow in this model (measured with radioactive microsphere techniques) may be reduced to 25 percent of normal ($P < 0.001$) by coronary stenosis and tachycardia while subepicardial flow remains normal. Epicardial S-T depression seems to indicate reciprocally subendocardial S-T elevation as long as a layer of nonischemic epicardial muscle is present, but when ischemia becomes transmural, epicardial S-T elevation occurs. Regional pressure-flow relations were determined as distal coronary pressure was reduced at a constant aortic pressure, heart rate and cardiac output. These relations revealed remarkably effective autoregulation of epicardial blood flow concomitant with progressive subendocardial ischemia.

Subendocardial infarction occurs when oxygen supply to the subendocardium is inadequate to meet oxygen demand. This discrepancy between supply and demand may be produced by a variety of experimental interventions such as coronary occlusion, coronary stenosis, aortic stenosis, arteriovenous fistula, anemia and inotropic stimulation.[1–8] S-T segment changes in epicardial, myocardial and intracavitary electrograms have been related to the presence of subendocardial ischemia.[9–12] In this study we evaluated S-T segment evaluation in subendocardial electrograms as a method of detecting subendocardial ischemia. Graded circumflex coronary arterial stenosis was used to limit oxygen supply, and S-T segment changes were correlated with both regional blood flow (measured with radioactive microsphere techniques) and morphologic evidence of necrosis.

Methods

Instrumentation and measurements: Experiments were conducted in American foxhounds from the National Institutes of Health dog colony. Anesthesia was induced with intravenously administered sodium thiamylal and maintained using mechanical ventilation with a mixture of halothane, oxygen and carbon dioxide. Arterial pH and partial pressure of carbon dioxide were maintained within physiologic range (range 7.30 to 7.50 and 25 to 50 mm Hg, respectively), and the partial pressure of oxygen ranged between 250 and 500 mm Hg. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. Six epicardial electrodes spaced 5/16 inch (0.79 cm) apart on a rubber band[9,10] were positioned parallel to and 1.5 cm inferior to the circumflex coronary artery on the posterior wall of the heart. Subendocardial electrodes, fashioned from 0.007 inch (0.018 cm) Teflon®-coated stainless steel wires hooked at one end[9,10] were plunged through the ventricular wall within a 25 gauge needle and then hooked back into the subendocardium. The exposed tip of the electrode was thereby positioned 1 to 2 mm from the ventricular cavity. Each subendocardial electrode was placed beneath an epicardial electrode. Thus a linear array of six pairs of epicardial and subendocardial electrodes was placed within the area of distribution of the circumflex artery. Electrocardiograms were recorded

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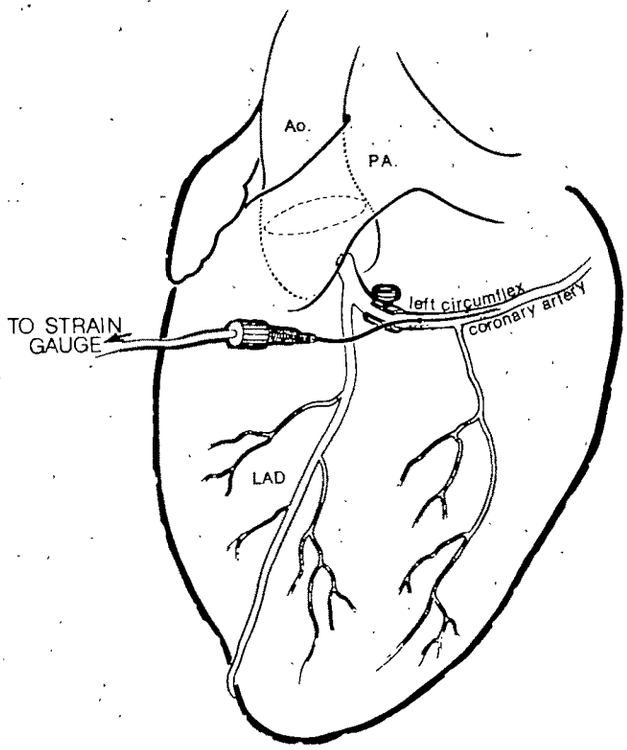


FIGURE 1. Diagram showing the miniature plastic screw clamp placed on the proximal left circumflex coronary artery. Distal coronary pressure was measured through a 20 gauge catheter placed just distal to the stenosis. Ao. = aorta; LAD = left anterior descending coronary artery; P.A. = pulmonary artery.

from the electrodes using the unipolar lead of a standard electrocardiographic amplifier. Because currents of injury required 30 to 45 minutes to stabilize, electrodes were placed at the beginning of each experiment, allowing at least 1 hour to elapse between electrode placement and control recordings. S-T segment levels were determined 100 msec after the onset of the QRS complex.

The first centimeter of the left circumflex coronary artery was isolated. A miniature plastic screw clamp (Fig. 1) that moved freely with the artery allowed the imposed resistance to remain constant during the cardiac and respiratory cycles. A no. 20 Teflon catheter was inserted into the distal circumflex artery. Blood pressure (aortic arch by way of the left axillary artery) and distal coronary pressure were measured in each experiment using strain gauges calibrated simultaneously with a single hydraulic system. A bipolar atrial pacing wire was attached for control of heart rate.

In some animals hemodynamic variables were precisely controlled using an aorto-right atrial shunt system that has previously been described.[13,14] Briefly, a portion of the aortic blood flow was diverted through cannulation of the brachiocephatic artery into a flow-through shunt reservoir inside a pressure bottle. Shunt flow was directed back into the right atrium through a large-bore external jugular cannula. Aortic pressure could be controlled within 2 mm Hg by adjustment of air pressure within the pressure bottle. Either cardiac output or left atrial pressure could be controlled by adjusting flow from the shunt reservoir into the right atrium. Ascending aortic flow was measured with an electromagnetic flowmeter (Statham Medical Instruments, Hato Rey, Puerto Rico). Dense spinal anesthesia was produced by injection of tetracaine hydrochloride, 40 mg, into the cisterna magna. Massive vasodilatation, which signaled the onset of spinal anesthesia, was reversed with catecholamine infusion (epinephrine, 0.67 μg/min; norepinephrine, 1.33 μg/min; and methoxamine, 20 μg/min).[13,14] Thus, in these animals, cardiac output (or left atrial pressure) and aortic pressure were controlled with the shunt system, heart rate was controlled with atrial pacing and adrenergic tone was maintained constant with spinal anesthesia using catecholamine infusion.

Regional myocardial blood flow: This was measured with a radioactive microsphere technique.[15–17] Radionuclide-labeled microspheres, large enough to be trapped in capillary networks and small enough to simulate red cell flow, were injected in a bolus dose into the left atrium. The spheres were mixed in the turbulent left ventricular cavity and then ejected to lodge in systemic capillaries. A constant arterial withdrawal (at a rate of 10 ml/min, for example), begun just before injection, continued until the microspheres disappeared from the circulation. The radioactivity in this reference sample was equal to the radioactivity that should be trapped in a systemic capillary network that filters a similar volume of blood per minute (10 ml/min). Similarly, flow in a myocardial sample may be calculated by the formula:

$$\frac{\text{ml/min in myocardial sample}}{\text{ml/min in reference sample}} = \frac{\text{myocardial radioactivity}}{\text{reference radioactivity}}$$

Several microsphere flow measurements in a single experiment were possible because the energy pattern of the gamma emission of each radionuclide (as detected with a sodium iodide crystal in a scintillation counter) was separable by mathematical analysis from the unique patterns of the other radionuclides.

In this study, 15 ± 5 (mean ± standard error of the mean) μ microspheres labeled with chromium-51, strontium-85, cerium-141 or ytterbium-169 (Minnesota Mining and Manufacturing Company, Minneapolis, Minnesota) were used; 400,000 to 2 million microspheres were injected in each bolus dose. A 1 minute reference collection was made with use of a nonocclusive catheter in the femoral artery. Subsequent arterial collections verified disappearance of 97 percent of the microspheres during the reference collection. Two sections of myocardium, each clearly within the distribution of the left anterior descending or left circumflex coronary artery, were selected for analysis. Each section was sliced into thirds from endocardium to epicardium (or into four layers in later portions of the study). Blood flow in each layer was then calculated with the reference sample technique described with the aid of an automated scintillation counter and computer analysis. Each sample was estimated to contain at least 400 microspheres, a quantity that Buckberg et al.[16] have suggested is adequate to ensure reproducibility with this technique.

Experimental protocol: Preliminary experiments in five dogs demonstrated that graded circumflex stenosis with tachycardia (150 to 200 beats/min) reproducibly caused subendocardial S-T segment elevation at higher levels of distal coronary pressure than those at which epicardial S-T elevation occurred. A four part experimental protocol was designed to study the significance of these changes with regard to morphologic sequelae, regional blood flow and epicardial S-T segment depression:

1. *Morphologic sequelae* were studied in eight dogs. Under sterile conditions a combination of tachycardia (heart rate 100 to 200 beats/min) and left circumflex arterial stenosis was used to evoke subendocardial S-T elevation without epicardial S-T elevation for 3 hours. The hemodynamic controls were then removed and the animals allowed to recover. Surviving ani-

mals were killed 11 to 28 days after operation for morphologic examination.

2. *Regional flow studies* were conducted in five animals without hemodynamic control. After control hemodynamic and microsphere measurements were made, tachycardia and coronary stenosis were used to evoke the combination of subendocardial S-T elevation and epicardial S-T depression. After 5 minutes, repeat hemodynamic and microsphere measurements were made. At 10 minutes tachycardia and stenosis were abolished and final measurements were made 1, 2 or 4 minutes later. In this section, flow measurements were made in the inner and outer thirds of the myocardium.

3. *The relation between subendocardial S-T elevation and epicardial S-T depression* was studied in six experiments with careful hemodynamic control using the aorto-right atrial shunt system described. At a constant heart rate (150 beats/min), mean aortic pressure (100 mm Hg) and cardiac output in each dog (range 0.9 to 1.8 liters/min), distal coronary pressure was reduced every 3 minutes in steps of 10 mm Hg from 80 to 40 mm Hg. At each step S-T segment changes were recorded.

4. Finally, *regional blood flow at various levels of distal coronary pressure* was measured in 17 dogs (some of which were also used in another experiment[18]) under controlled hemodynamic conditions (heart rate 150 beats/min, mean aortic pressure 100 mm Hg and cardiac output 0.9 to 2.8 liters/min) similar to those imposed in section 3. In this section, flow was measured in the inner and outer fourths of the myocardium rather than the endocardial and epicardial thirds as in section 2.

Statistical analysis was performed using the t test for paired or nonpaired data as appropriate. Data are reported as mean ± standard error of the mean.

Results

1. Morphologic sequelae: Coronary stenosis sufficient to achieve endocardial S-T elevation without epicardial S-T elevation was maintained for 3 hours in eight animals (Table I). Atrial pacing was utilized in six of the eight dogs. Endocardial S-T elevation increased and epicardial S-T segments tended to be progressively depressed during the 3 hour period. In the two dogs not subjected to pacing, heart rate ranged from 100 to 133 beats/min during the study period. In these two dogs, results were qualitatively similar to those in the other six dogs, but the distal coronary pressure that led to partial thickness ischemia tended to be lower (34 mm Hg at 5 minutes, 30 mm Hg at 3 hours).

The coronary stenosis was released at the end of the 3 hour period and the animals were allowed to recover.



FIGURE 2. Morphologic appearance of a full thickness section from the left circumflex coronary arterial distribution 14 days after 3 hours of coronary stenosis. In this photograph of a Masson trichrome stain, necrotic areas of the lower (subendocardial) portion of the section appear lighter than the normal muscle in the subepicardium.

Arrhythmias were common upon reperfusion and precluded S-T segment evaluation in four of the eight dogs. Reperfusion in the four whose S-T segment changes could be estimated led to a diminution of subendocardial S-T elevation ($\Delta\overline{ST}$ 0.67 to 0.22 mv, $P < 0.05$), but the subendocardial S-T elevation that persisted after 10 minutes of reperfusion was still significantly above control levels ($P < 0.01$).

All eight dogs recovered from anesthesia and were returned to their cages. Two had persistent ventricular arrhythmias and died within 36 hours of operation. A third died 3 days after operation. The other five were killed 11 to 28 (mean 16.4) days after operation. Gross examination of all eight hearts invariably revealed patchy subendocardial necrosis. The tip of the posterior papillary muscle was necrotic in every dog. Extension of necrosis to the epicardium occurred only along the tracts of the subendocardial electrodes that had been left in place. Histologic examination verified the absence of epicardial necrosis (Fig. 2).

2. Regional flow during partial occlusion with tachycardia: In five dogs, rapid atrial pacing was instituted and coronary occlusion was adjusted to cause

TABLE I

Summary of Hemodynamic and S-T Segment Changes (mean ± standard error of the mean)

	Distal Coronary Pressure (mm Hg)	Heart Rate (beats/min)	Aortic Pressure (mm Hg)	$\Delta\overline{ST}$ (mv)	
				Endocardial	Epicardial
Before stenosis	115 ± 5	133 ± 7	115 ± 5	0	0
5 minutes of stenosis	46 ± 5†	170 ± 14*	112 ± 4	1.3 ± 0.1†	0.1 ± 0.2
3 hours of stenosis	45 ± 4	178 ± 12	98 ± 5	1.9 ± 0.2*	−0.4 ± 0.3

* $P < 0.05$ compared with above value (no. = 8).
† $P < 0.01$ compared with above value (no. = 8).
ΔST = the average S-T segment change per electrode in six epicardial or endocardial electrodes.

TABLE II

Hemodynamics and S-T Segment Changes During and After Coronary Stenosis and Tachycardia

	Aortic Pressure (mm Hg)	Distal Coronary Pressure (mm Hg)	Left Atrial Pressure (mm Hg)	Heart Rate (beats/min)	$\Delta\overline{ST}$ (mv)	
					Endocardial	Epicardial
Before stenosis	111 ± 6	110 ± 6	5.2 ± 1.4	121 ± 5	0	0
After 5 minutes of stenosis	86 ± 5†	50 ± 6†	14 ± 2.8†	196 ± 4†	2.5 ± 0.5†	−0.7 ± 0.2*
5 minutes after release	102 ± 3†	102 ± 3†	‡	122 ± 7†	0.2 ± 0.2†	0.02 ± 0.2*

* $P < 0.05$ compared with above value (no. = 5).
† $P < 0.01$ compared with above value (no. = 5).
‡ Poststenosis left atrial pressure was measured in only three dogs. In these three dogs left atrial pressure after release returned to prestenosis levels.
$\Delta\overline{ST}$ = the average S-T segment change per electrode in six epicardial or endocardial electrodes.

endocardial S-T elevation and epicardial S-T depression (Table II). After a 10 minute ischemic period, the arterial constrictor was released, pacing was discontinued and S-T segments were returned to control levels. This combination of stenosis and tachycardia also caused a reduction in mean aortic pressure and an elevation of mean left atrial pressure (Table II).

Radioactive microspheres were injected before stenosis, after 5 minutes of stenosis and 1 to 4 minutes after release of stenosis. Stenosis with tachycardia caused a marked decrease in flow to the inner third (endocardium) of the ischemic area (1.00 ± 0.01 to 0.24 ± 0.04 ml/g per min, $P < 0.001$) whereas flow to the outer third (epicardium) was unchanged (0.90 ± 0.13 to 0.99 ± 0.13 ml/g per min [difference not significant]). Flow increased in both the epicardium and the endocardium in the nonischemic area (Fig. 3). Upon termination of stenosis and tachycardia, reactive hyperemia was observed. In the dog that received the injection 1 minute after release of the stenosis, epicardial flow was greater than endocardial flow. But by 2 to 4 minutes after release, endocardial flow (average 2.8 ± 1.9 ml/g per min) greatly exceeded epicardial flow (average 1.18 ± 0.20) ($P < 0.05$, Fig. 4).

3. S-T elevation in a hemodynamically controlled preparation: Partial coronary occlusion was studied in six dogs whose blood pressure, cardiac output and heart rate were controlled with the aorto-right atrial shunt system previously described (Fig. 5). As distal coronary pressure was decreased, S-T elevation in the subendocardial electrogram was progressive. Epicardial S-T depression increased progressively until a critical level of coronary pressure was reached. At this point, epicardial S-T elevation rapidly ensued.

4. Changes in regional flow as distal coronary pressure was progressively reduced: In this section, microsphere estimation of regional myocardial blood flow was combined with the hemodynamic controls used

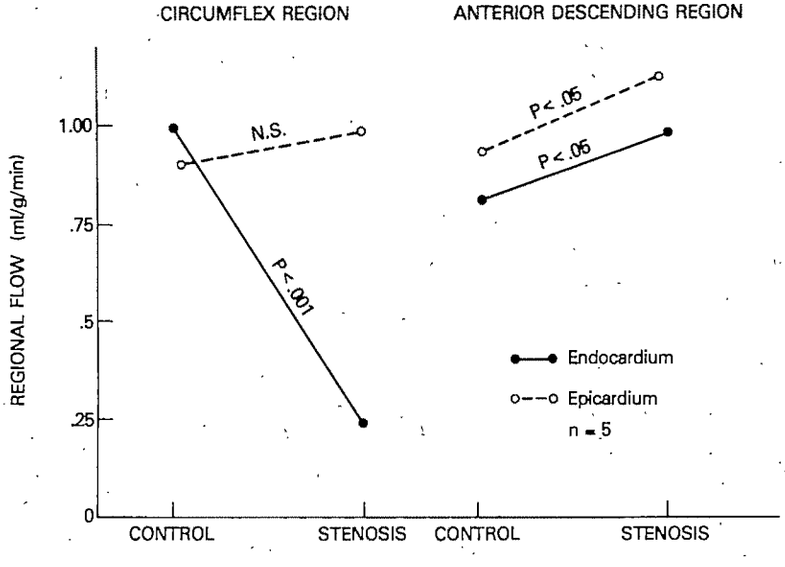


FIGURE 3. Regional flow determinations after 5 minutes of coronary stenosis with endocardial S-T elevation and epicardial S-T depression. N.S. = difference not significant; P = probability.

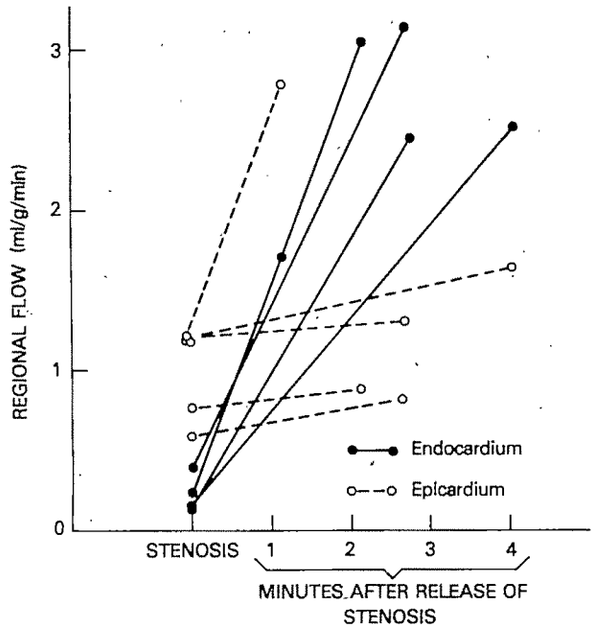


FIGURE 4. Regional reactive hyperemia after release of a stenosis causing endocardial S-T elevation and epicardial S-T depression. After 2 minutes, endocardial hyperemia persists, but epicardial flow has returned to control levels.

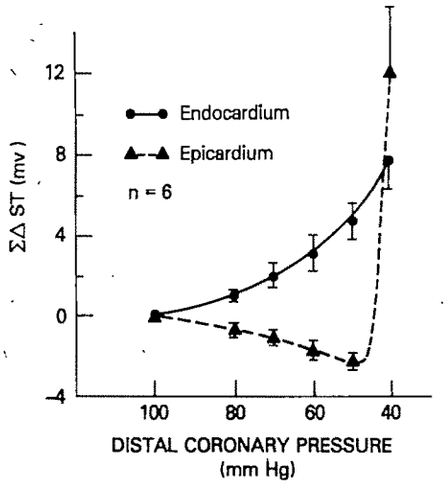


FIGURE 5. S-T alterations in endocardial and epicardial electrodes as distal coronary pressure is reduced at constant aortic pressure (100 mm Hg), heart rate (150 beats/min) and cardiac output (constant in each experiment, range 0.9 to 1.8 liters/min). $\Sigma\Delta ST$ is the sum of S-T segment changes in six endocardial (**closed circles**) or epicardial (**closed triangles**) electrodes.

in the preceding section. Flow was measured in the inner and outer fourths of the myocardium. These studies resulted in 53 determinations of regional flow at various distal coronary pressures. Right atrial pressure (usually 1 to 3 mm Hg) has been subtracted from distal coronary pressure in this section. Over a distal coronary pressure range of 30 to 70 mm Hg a highly significant linear relation was observed between distal coronary pressure (CP) and normalized flow to the subendocardium (inner fourth of the ventricular wall) of the ischemic area: $Q_{CxN}/Q_{LAD} = 0.0239\ CP - 0.638$ ($r = 0.93$, $P < 0.001$) (Fig. 6). Each endocardial flow measurement (Q_{CxN}) was normalized by dividing by the simultaneous flow in the nonischemic area (Q_{LAD}), where Q_{CxN} = subendocardial area perfused by the left circumflex artery and Q_{LAD} = area perfused by the left anterior descending coronary artery. Flow to the epicardial portion of the ischemic area, similarly normalized, was maintained at near

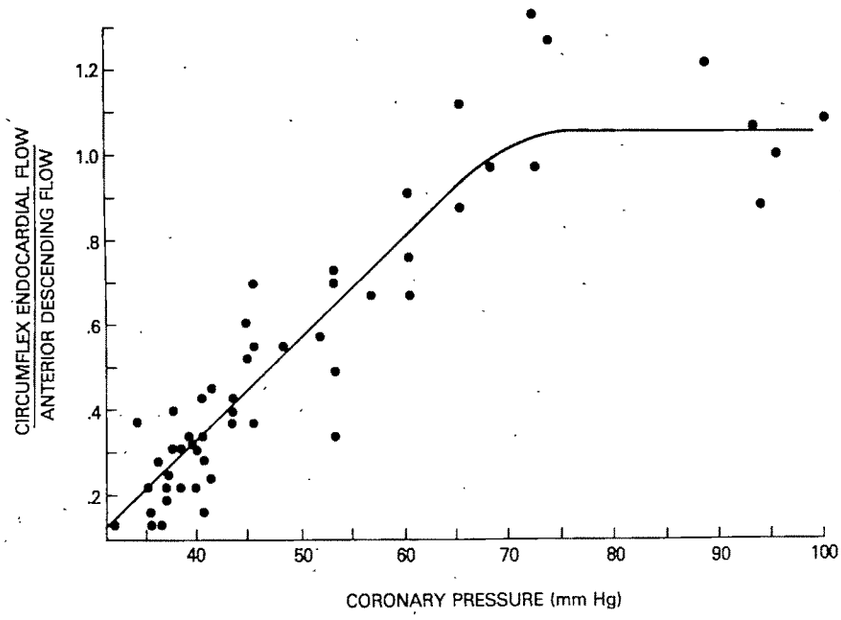


FIGURE 6. Relation between distal coronary pressure and regional flow to the endocardial fourth of the ischemic circumflex area, normalized by dividing by the simultaneous flow in the nonischemic area of the left anterior descending coronary artery. Over a pressure range of 30 to 70 mm Hg a linear relation was observed between these two variables ($r = 0.93$, $P < 0.001$).

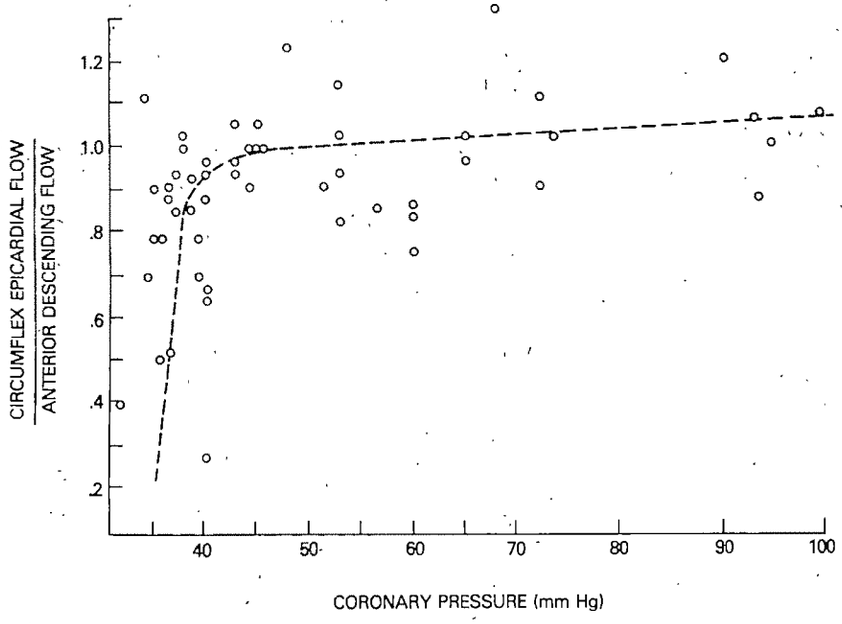


FIGURE 7. Relation between distal coronary pressure and regional flow to the epicardial fourth of the myocardium, normalized by dividing by the simultaneous flow in the nonischemic area.

normal levels until distal coronary pressure fell below about 40 mm Hg. Below 40 mm Hg, epicardial flow decreased precipitously (Fig. 7). The similarity between the relation of regional flow to coronary pressure and the relation of S-T elevation to coronary pressure (Fig. 5) is striking. A preliminary report of this observation, based on a smaller number of flow determinations, was made in a recent review article.[19]

Discussion

Correlation of subendocardial S-T elevation, epicardial S-T depression and subendocardial necrosis: Subendocardial S-T segment elevation, caused by coronary stenosis and tachycardia and sustained for 3 hours, invariably led to subsequent subendocardial necrosis in this study. Such necrosis occurred without epicardial S-T segment elevation. Therefore, although epicardial S-T elevation is clearly related to local ischemia,[1,20–24] the absence of epicardial S-T elevation does not guarantee the absence of underlying ischemia.[22,25–28] Indeed, epicardial S-T segments were not elevated in this study during coronary stenosis that was sufficiently restrictive to reduce subendocardial blood flow to 25 percent of normal (Fig. 3).

A reciprocal relation was observed between epicardial S-T depression and subendocardial S-T elevation in these experiments. Such a reciprocal relation was suggested by Wolferth et al.[11] and Hellerstein and Katz[12] in studies of mechanical myocardial injury. However, Prinzmetal and colleagues[29,30] suggested that epicardial S-T depression is the direct result of mild local ischemia causing an increased epicardial intracell negativity, but they did not perform direct measurement of local myocardial blood flow. Regional flow measurements in our experiments revealed that epicardial S-T depression was associated with normal flow to the epicardium and decreased blood flow to deeper myocardial layers (Fig. 3, 5, 6 and 7). When ischemia became transmural and there was no longer a layer of normal muscle between the epicardial electrode and the injured myocardium, epicardial S-T elevation occurred (Fig. 5 and 7). As predicted by Prinzmetal et al.[30] from electrophysiologic considerations, the magnitude of this reciprocal S-T depression is small compared with the magnitude of simultaneous subendocardial S-T elevation.

Factors increasing vulnerability of subendocardium to diminished blood flow: The subendocardium is unusually vulnerable to limitation of coronary inflow. This has been demonstrated with both acute coronary occlusion[6,31–33] and coronary stenosis.[5,7,34,35] The vulnerability of the subendocardium is related to mechanical and hemodynamic factors that limit systolic flow to the inner layers of the myocardium. Intramyocardial pressure in these layers equals or exceeds aortic pressure during systole.[36,37] These compressive forces greatly retard systolic blood flow in the inner layers of the heart.[36,38] Because subendocardial flow is limited mainly to diastole and regional flow is normally homogeneous, regional flow in diastole in the subendocardium must be greater than diastolic flow in the subepicardium (because the subepicardium also has systolic flow). It follows that regional resistance to diastolic flow must be lower in the subendocardium than in the subepicardium. Studies of the blood content of small vessels in the left ventricle have indeed revealed a greater density of open capillaries in the deep layers compared with the superficial layers. But as coronary hypotension is induced and vessels in all layers begin to dilate, this subendocardial-less-than-subepicardial resistance ratio cannot be maintained because the reserve of unopened capillaries does not seem to be greater in the subendocardium than in the subepicardium.[39] A level of coronary pressure will be reached below which

homogeneous flow cannot be maintained because the subendocardial system is maximally dilated and dilatory reserve remains in the subepicardium. In our study, this level of coronary pressure was about 70 mm Hg (Fig. 6), but different hemodynamic and inotropic conditions would tend to alter the coronary pressure at which the subendocardial vasculature is maximally dilated.

Coronary pressure and regional myocardial flow: The great discrepancy in regional blood flow that occurs with coronary hypotension favors preservation of the subepicardium and sacrifice of the subendocardium. Indeed, a fixed proximal coronary stenosis allows the subepicardium to "steal" perfusion from the subendocardium. As the subepicardial vasculature dilates in response to metabolic demands, coronary pressure distal to a proximal stenosis decreases and may cause hypoperfusion of the subendocardium in which the dilatory reserve may be exhausted.[8,40] Flameng et al.[35] injected a potent coronary vasodilator, dipyridamole, into dog hearts compromised by a circumflex arterial stenosis. Dipyridamole caused a further maldistribution of perfusion in the circumflex region as the dilatory reserve of the subepicardium allowed a steal of perfusion from the subendocardium. This steal effect is greatest over that range of distal coronary pressures in which dilatory reserve persists in the subepicardium but is depleted in the subendocardium. Under the hemodynamic conditions used in our study, this range is 40 to 70 mm Hg (Fig. 6 and 7).

The regional flow patterns obtained during reactive hyperemia (Fig. 4) deserve comment. Marked epicardial hyperemia and moderate endocardial hyperemia occurred in the single animal that received an injection 1 minute after release of stenosis. Two minutes after release, epicardial flow had returned to normal but endocardial hyperemia was prominent. These findings suggest that the epicardium is able to satisfy its hyperemia flow demand, whatever the origin of that demand may be,[41,42] before maximal flow to the subendocardium occurs. Perhaps this is also a form of coronary steal, a "high flow" steal with maximal dilation in both areas causing relative overperfusion of the subepicardium. Endocardial reactive hyperemia persists up to 4 minutes after release of the stenosis and demonstrates that subendocardial hyperperfusion may occur in the absence of subepicardial hyperperfusion.

Clinical implications: Acute coronary occlusion in animals cannot closely simulate human myocardial ischemia because coronary disease is progressive in man and collateral vessels usually have time to develop. But the experimental model used in this study, ischemia produced by graded coronary hypotension and detected with subendocardial electrograms, provides a wide spectrum of experimental states within which conditions similar to those in man may be found. The electrophysiologic, regional flow and morphologic sequelae of graded coronary stenosis in our study emphasize an important concept: Although regional coronary blood flow is normally homogeneous, regional vulnerability to limitation of coronary inflow is distinctly heterogeneous. Moreover, coronary vasculature is so structured that alterations in epicardial flow may affect endocardial perfusion. These concepts seem less important when total coronary occlusion in the absence of abundant collateral vessels causes massive transmural infarction, but they may be critical in myocardial ischemia caused by subtotal occlusion or by complete occlusion in the presence of well developed collateral vessels.

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Evolution of Regional Ischemia Distal to a Proximal Coronary Stenosis: Self-Propagation of Ischemia

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The temporal evolution of myocardial ischemia was studied in open chest dogs at constant preload, afterload and heart rate. In one group of animals, a variable circumflex arterial stenosis was used to maintain constant distal circumflex arterial hypotension (40 to 50 mm Hg). During a 3 hour period of stenosis, flow in the subendocardial fourth of the ischemic ventricular wall decreased from 0.22 to 0.09 ml/g per min ($P < 0.02$), whereas subepicardial flow was not significantly changed. Local vascular resistance, therefore, doubled in the most ischemic area of myocardium. In a second group of animals in which proximal coronary stenosis was held constant and pressure varied, an ischemia-mediated increase in local vascular resistance was also demonstrated. In addition, a reciprocal relation was observed between changes in flow in the left anterior descending coronary region and changes in collateral flow to the region of the circumflex artery. A coronary steal mechanism and an ischemia-mediated resistance increase may be two means by which ischemia is self-propagating.

The fate of severely ischemic myocardium is dependent upon an evolving balance between local blood flow and the tissue's need for perfusion. Within the heart, the development of collateral flow may be rapid,[1,2] local swelling of the cells may retard myocardial perfusion[3–5] and the collateral and intramural vascular networks may provide a complex system of vascular resistances so that changes in flow in one region alter flow in an adjacent or distant region.[6–8] Superimposed upon this intrinsic system are the hemodynamic determinants of myocardial perfusion that may alter both oxygen demand (and thereby local vascular resistance) and potential oxygen supply. In this study, we attempted to isolate the intrinsic system for perfusion of ischemic myocardium by controlling the extrinsic hemodynamic determinants of regional perfusion. In a previous investigation,[8a] we developed a model of circumflex coronary arterial stenosis that reproducibly evokes subendocardial ischemia while epicardial perfusion is maintained. Such stenosis provides a large ischemic region containing subregions in which perfusion ranges from very low to nearly normal. Temporal changes in regional blood flow in these subregions were studied under two conditions: (1) constant distal circumflex arterial hypotension, and (2) constant proximal circumflex arterial stenosis (allowing distal circumflex pressure to vary). Two characteristics of the intrinsic system for perfusion of ischemic myocardium were suggested by these investigations: (1) a time-related increase in regional vascular resistance in severely ischemic myocardium, and (2) a possible coronary steal phenomenon, that is, a reciprocal relation between changes in regional flow in the donor area and changes in collateral flow to the ischemic area.

Methods

Experiments were conducted in 18 American foxhounds. Anesthesia was induced with sodium thiamylal and maintained by ventilation with a mixture of

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halothane, oxygen and carbon dioxide. Constant end-expiratory pressure (5 cm water) was utilized to prevent lung collapse after the chest was opened. Arterial blood gases and hematocrit were maintained within physiologic range throughout the experiments (with the exception of P_{O_2}, partial pressure of oxygen, which ranged from 250 to 500 mm Hg).

An aorto-right atrial shunt system, as described previously,[9,10] was used to control hemodynamic variables. Briefly, aortic pressure and left atrial pressure were controlled with an adjustable flow-through pressure bottle in the shunt system, heart rate was controlled with atrial pacing and autonomic tone was held constant with dense spinal anesthesia and catecholamine infusion. Aortic pressure, left atrial pressure, right atrial pressure and distal left circumflex arterial pressure were measured through short polyethylene catheters, and the first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation of the output from a solid state pressure transducer (Edwards Laboratory, Santa Ana, California) in the left ventricle. Aortic flow was measured with use of an electromagnetic flowmeter (Statham Medical Instruments, Inc., Hato Rey, Puerto Rico) on the ascending aorta. Subendocardial and epicardial electrograms were recorded from a linear array of six pairs of electrodes in the area of distribution of the left circumflex coronary artery. A variable constricting device was positioned on the proximal circumflex artery.

Regional blood flow was measured with 15 ± 5 (mean ± standard error of the mean) radioactive microspheres (chromium-51, strontium-85, cerium 141, ytterbium-169) using a reference arterial sample to calculate absolute flows.[8a] Myocardium from both the anterior descending and circumflex coronary arterial regions was sliced into four layers—inner, outer, subinner and subouter. The subouter area ranged from 1 to 3 mm among various animals whereas the other three layers were consistently sliced 2.0 to 2.5 mm in thickness. Regional flow was thus calculated in eight regions in each experiment. Each sample had a calculated microsphere content of at least 400 spheres.

In the first series of experiments, a variable proximal circumflex coronary arterial stenosis was used to create partial thickness ischemia with constant distal circumflex pressure. After baseline hemodynamic measurements had been completed and regional flow measured in the control state, coronary stenosis was created that was sufficiently severe to cause subendocardial S-T elevation with minimal or no epicardial S-T elevation. This initial level of distal coronary pressure, at which partial thickness ischemia initially occurred, was about 40-mm Hg. Because distal coronary pressure generally increased with time, the initial pressure was restored (within 1 to 2 mm Hg) by readjusting the stenosis at 15 and 30 minutes, and every 30 minutes thereafter for 3 hours. If marked epicardial S-T elevation occurred, coronary stenosis was adjusted to effect a 5 mm Hg increase in coronary pressure, which invariably abolished epicardial S-T elevation. Radioactive microspheres were injected after 5 minutes and 3 hours of stenosis. If epicardial S-T segments had become elevated during the experiment and coronary pressure had been increased during the 3 hours, the latter was reduced back to the initial level for at least 5 minutes before the microsphere injection. The stenosis was then released and a final microsphere injection made after 30 minutes of reperfusion.

In the second group of experiments, proximal left circumflex arterial stenosis was constant and distal circumflex pressure was allowed to vary. After control hemodynamic measurements were recorded, the left circumflex coronary artery was partially occluded in order to decrease distal circumflex pressure just beyond the point at which epicardial S-T segments began to rise; that is, transmural ischemia was created. Circumflex coronary arterial constriction was left unaltered for the remainder of the study period. Regional flow was measured 5, 30, 90 and 180 minutes after stenosis. If cardiac function deteriorated with time, cardiac output was decreased (that is, shunt flow was decreased) to keep left atrial pressure constant. Mean aortic pressure was constant (range 97 to 102 mm Hg) and the atria were paced at 150 beats/min for the entire 3 hour period. Data were collected from 12 animals. Three experiments yielded incomplete data: One animal had mechanical alternans during the last hour of ischemia, another animal manifested hives, flushing and marked vasodilation after 1 hour of ischemia and a third animal was mistakenly given two injections of the same radionuclide at 5 and 30 minutes after stenosis. Thus, 11 animals were studied completely during the first 30 minutes, 10 had complete hemodynamic data for the full 3 hours and 9 had regional flow data for the 3 hour period.

Statistical analysis was performed using the *t* test for paired or unpaired data as appropriate. Data are expressed as mean ± standard error of the mean unless otherwise noted.

Results

Constant Distal Circumflex Pressure

Hemodynamic changes (Table I): Experiments were conducted in six animals, but one dog that manifested ventricular arrhythmias was excluded from analysis. Aortic pressure was constant at 100 mm Hg (range 99 to 101), and heart rate was 150 beats/min (atrial pacing) for all parts of the study. Ventricular function was not changed by the stenosis in the first 5 minutes but deteriorated over the 3 hour period as evidenced by a decrease in cardiac output and dP/dt and an increase in left atrial pressure. As ventricular function

TABLE I

Hemodynamic Changes During Circumflex Stenosis in Five Preparations (mean ± standard error of the mean)

	Aortic Flow (liters/min)	Pressures (mm Hg)			dP/dt (mm Hg/sec)	ΣΔST*	
		Right Atrial	Left Atrial	Circumflex		Endocardial	Epicardial
Prestenosis	1.64 ± 0.15	2.7 ± 1.1	4.2 ± 0.6	97.4 ± 1.3	2209 ± 181	...	...
After 5 minutes of stenosis	1.58 ± 0.13	2.6 ± 1.1	4.8 ± 0.9	41.4 ± 0.9‡	2359 ± 92	4.2 ± 0.9‡	0.8 ± 1.2
After 3 hours of stenosis	1.33 ± 0.12†‡	2.9 ± 0.9	8.1 ± 0.6†‡	42.2 ± 0.9‡	1922 ± 109†	8.7 ± 3.5	3.4 ± 3.1
After 30 minutes of reperfusion	1.39 ± 0.10	3.0 ± 0.9	6.5 ± 0.4†‡	98.8 ± 4.3†	1791 ± 113	2.3 ± 1.2	−2.0 ± 0.7‡

* ΣΔST is the sum of S-T segment changes in six electrodes (four studies in endocardial and five in epicardial tissue).
† $P < 0.05$ compared with value above.
‡ $P < 0.05$ compared with the value before stenosis.

changed, cardiac output was decreased (that is, the aorto-right atrial shunt was decreased) to prevent large changes in left atrial pressure. Left atrial pressure increased only an average of 3.3 mm Hg during the stenosis. Reperfusion led to no significant change in ventricular function.

S-T segment changes: Coronary stenosis evoked S-T elevation in the subendocardial electrograms of all animals. Because severe ischemia of the subendocardium was more important to this study than maintenance of normal subepicardial flow, distal coronary pressure was reduced *beyond* the point of maximal epicardial S-T depression to the pressure at which epicardial S-T segments had returned to 0. Coronary stenosis was adjusted over the first 5 minutes to effect these S-T changes and the microspheres were then injected. Distal coronary pressure increased an average of 14.6 mm Hg over the ensuing 10 minutes before the coronary stenosis was altered to restore the initial pressure. Over the next 15 minutes, coronary pressure increased an average of 5.4 mm Hg before initial pressure was restored at 30 minutes. After 30 minutes, distal coronary pressure was quite stable and the average total increase over the remaining 2 1/2 hours was only 5.4 mm Hg.

Sustained partial thickness ischemia was the goal of this preparation. The occurrence of average epicardial S-T elevation greater than 1 mv was interpreted as evidence of transmural ischemia. Distal coronary pressure was elevated to 5 mm Hg above the initial pressure if transmural S-T elevation occurred. Epicardial S-T elevation was invariably eliminated by this maneuver. Such elevation was necessary in two animals 30 minutes and 2 hours, respectively, after stenosis. In both animals, the initial pressure was restored before the injection of microspheres 3 hours after stenosis.

Subendocardial S-T segment changes could be evaluated in only four animals. In one animal excluded from this analysis the subendocardial electrodes were placed too close to the atrioventricular groove and three of the six electrodes were hooked on chordae tendineae. Endocardial S-T elevation tended to increase over the 3 hour period of stenosis, and release of the stenosis restored endocardial S-T segments toward control levels (Table I).

Regional flow and resistance: The first 5 minutes of coronary stenosis effected a marked reduction in subendocardial flow and a moderate reduction in subepicardial flow (Table II). After 3 hours of ischemia, further decreases in subepicardial flow (a 14 percent reduction) were not significant whereas a 59 percent ($P < 0.02$) reduction in flow ensued in the more ischemic subendocardium. Release of stenosis restored flow in both areas to prestenosis levels.

Regional coronary resistance (Table II, Fig. 1) more than doubled in the subendocardial layer over the 3 hour period but was unchanged in the subepicardial layers. Thirty minutes after the release of stenosis, regional resistance had returned to prestenosis levels. Intermediate layers of myocardium exhibited intermediate changes in resistance. Regional resistance in the area of the nonischemic left anterior descending coronary artery was unchanged during the 3 hour period.

Constant Proximal Coronary Stenosis

Infarcting and recovering subgroups: In all animals during the first 30 minutes of coronary arterial stenosis, perfusion of the ischemic area improved, epicardial S-T elevation

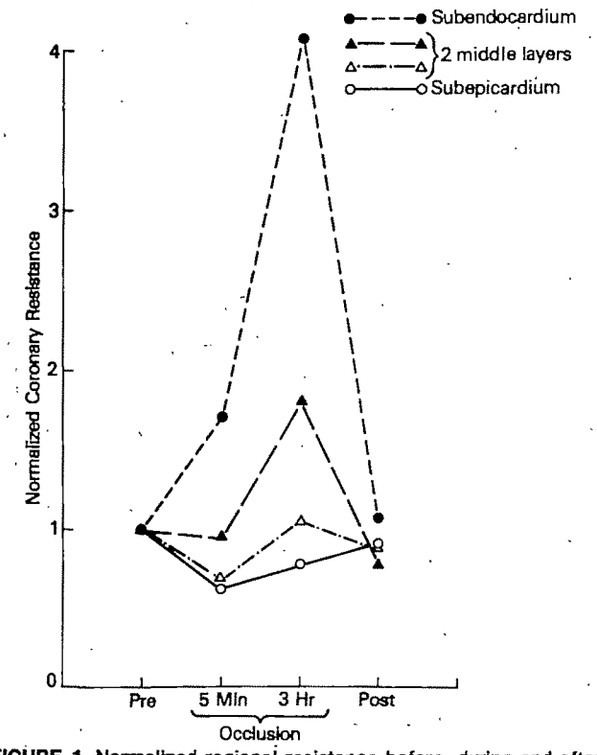


FIGURE 1. Normalized regional resistance before, during and after coronary stenosis in the ischemic (circumflex artery) region of the left ventricle. Resistance is normalized by assigning a value of 1 to prestenosis regional resistance in each layer.

TABLE II

Changes in Regional Flow and Resistance During Stenosis of the Circumflex Coronary Artery in Five Preparations (mean ± standard error of the mean)

	Regional Flow (ml/g per min)					Regional Resistance (mm Hg/(ml/g per min)		
	Circumflex Endocardium	Circumflex Epicardium	Circumflex Transmural Average	Anterior Descending Transmural Average	Circumflex Endocardial/ Epicardial Flow Ratio	Circumflex Endocardium	Circumflex Epicardium	Circumflex Transmural Average
Prestenosis	0.86 ± 0.12	0.91 ± 0.16	0.85 ± 0.12	0.82 ± 0.11	0.94 ± 0.07	119 ± 16	115 ± 15	122 ± 18
After 5 minutes of stenosis	0.22 ± 0.04†	0.56 ± 0.04	0.39 ± 0.05†	0.76 ± 0.06	0.39 ± 0.08†	205 ± 40	71 ± 6	105 ± 14
After 3 hours of stenosis	0.09 ± 0.02*	0.48 ± 0.06	0.25 ± 0.04*	0.71 ± 0.06	0.19 ± 0.03	486 ± 0.87*†	87 ± 12	173 ± 29*
After 30 minutes of reperfusion	0.70 ± 0.08*	0.93 ± 0.13*	0.79 ± 0.08*	0.67 ± 0.03	0.78 ± 0.08*	128 ± 11*	101 ± 16	113 ± 11

* $P < 0.05$ compared with value above.
† $P < 0.05$ compared to prestenosis value.

TABLE III

Hemodynamic Changes (mean ± standard error of the mean)

Time After Stenosis (min)	Aortic Flow (liters/min)	Pressures (mm Hg)			dP/dT (mm Hg/sec)	S-T Elevation (mv)*	
		Left Atrial	Right Atrial	Coronary		Endocardial	Epicardial
				Recovering Group (no. = 5)			
Pre	2.3 ± 0.1	5.4 ± 0.4	2.6 ± 0.3	100.0 ± 0.6	3037 ± 173	0	0
5	2.2 ± 0.2	7.2 ± 0.5[1]	2.8 ± 0.3	41.2 ± 0.6[1]	2874 ± 204	5.6 ± 1.5[1]	27.9 ± 6.5[1]
30	2.4 ± 0.2	5.9 ± 0.3[2]	3.0 ± 0.3	55.0 ± 4.3[1,2]	3101 ± 277	6.1 ± 1.6[1]	0.9 ± 1.6[2]
90	2.3 ± 0.2	5.4 ± 0.2[2,3]	2.9 ± 0.3	59.2 ± 5.5[1,2]	3352 ± 257	9.3 ± 2.4[1,3]	−2.8 ± 1.9[2]
180	2.2 ± 0.1	6.3 ± 0.4[1]	3.5 ± 0.2[1,2]	65.8 ± 5.5[1,2]	3014 ± 278	4.5 ± 1.7[4]	−1.3 ± 1.3
				Infarcting Group (no. = 5)			
Pre	2.0 ± 0.2	6.4 ± 0.5	2.5 ± 0.4	97.0 ± 0.8[5]	2121 ± 166[5]	0	0
5	1.7 ± 0.2[1]	8.4 ± 0.6[1]	2.6 ± 0.4	39.2 ± 1.7[1]	2122 ± 160[5]	7.8 ± 1.9[1]	24.2 ± 11.6
30	2.0 ± 0.2[2]	7.6 ± 0.9	2.6 ± 0.4	57.2 ± 5.9[1,2]	2382 ± 187	1.6 ± 1.5	−2.0 ± 1.8
90	1.9 ± 0.1	7.3 ± 0.8	2.5 ± 0.7	53.2 ± 4.8[1,2]	2496 ± 127[1,5]	5.7 ± 2.0[1]	−7.2 ± 4.1
180	1.4 ± 0.2[1,3,4,5]	10.8 ± 2.5	4.1 ± 0.8[1,2,3]	43.6 ± 1.7[1,5]	1987 ± 184[4]	13.3 ± 3.9[1]	10.5 ± 11.4

* S-T elevation is the sum of S-T segment changes in six electrodes.

Superscripts 1, 2, 3 and 4 indicate that this value is significantly different ($P < 0.05$) from the corresponding value in line 1, 2, 3 or 4, respectively. The superscript 5 indicates that this value is significantly different ($P < 0.05$) from the corresponding value in the recovering group.

disappeared (that is, ischemia was no longer transmural) and distal coronary pressure increased. After 30 minutes, each animal showed either continued improvement or a gradual reduction in flow to the ischemic area. Inspection of the regional flow data revealed that the absolute level of transmural circumflex arterial area flow after 5 minutes of stenosis predicted the subsequent course in an individual animal. If transmural flow in the circumflex distribution averaged less than 0.48 ml/g per min after 5 minutes of stenosis, gradual deterioration after 30 minutes invariably occurred. If transmural flow at 5 minutes was greater than 0.48 ml/g per min, progressive improvement ensued and regional flow returned to near normal levels by 3 hours. For the purposes of analysis, therefore, it is convenient to consider these two subgroups separately. The group with progressive ischemia at the end of 3 hours will be designated the infarcting group (no. = 7). The group with near normal regional flow at 3 hours will be designated the recovering group (no. = 5).

Early adaptation to stenosis: In the first 30 minutes of coronary stenosis, both groups of animals were similar. Creation of stenosis decreased distal coronary pressure to about 40 mm Hg and caused endocardial and epicardial S-T segment elevation (Table III). Elevation of left atrial pressure (by about 2 mm Hg) at constant or decreased cardiac output and a constant dP/dt indicated some impairment of ventricular function with stenosis (Table III). Regional flow to the ischemic area was less at 5 minutes in the infarcting group (by definition), but the transmural distribution of flow was similar in the two groups (Table IV). Between 5 and 30 minutes after stenosis, distal coronary pressure increased to about 56 mm Hg, epicardial S-T elevation disappeared and ventricular function improved (Table III). Blood flow to the region of the circumflex artery increased whereas flow to the region of the left nonischemic anterior descending artery decreased. The increase in flow in the ischemic area was directed almost exclusively to the deeper layers (Table IV).

TABLE IV

Regional Flow Changes (in ml/g per min) (mean ± standard error of the mean)

Time After Stenosis (min)	Circumflex Endocardium	Circumflex Epicardium	Circumflex Transmural	Anterior Descending Transmural	Circumflex Endocardium/ Epicardium Flow Ratio
			Recovering Group (no. = 5)		
5	0.35 ± 0.05	0.93 ± 0.06	0.63 ± 0.08	1.1 ± 0.07	0.37 ± 0.03
30	0.65 ± 0.12[1]	0.89 ± 0.03	0.78 ± 0.07	0.93 ± 0.05[1]	0.73 ± 0.12[1]
90	0.61 ± 0.10[1]	0.86 ± 0.08	0.74 ± 0.07[1]	0.87 ± 0.12	0.75 ± 0.15
180	0.75 ± 0.13[1]	0.93 ± 0.07	0.86 ± 0.08[1]	0.91 ± 0.07[1]	0.82 ± 0.14[1]
			Infarcting Group (no. = 4)		
5	0.18 ± 0.03[4]	0.53 ± 0.05[4]	0.34 ± 0.03[4]	0.80 ± 10[4]	0.34 ± 0.04
30	0.39 ± 0.08[1]	0.61 ± 0.09[4]	0.52 ± 0.05[1,4]	0.69 ± 0.08[1,4]	0.70 ± 0.19
90	0.31 ± 0.05[1,4]	0.66 ± 0.09	0.48 ± 0.03[1,4]	0.69 ± 0.07	0.52 ± 0.14[1]
180	0.16 ± 0.04[4]	0.68 ± 0.09	0.39 ± 0.06[4]	0.82 ± 0.05[3]	0.24 ± 0.03[4]

Superscripts 1, 2 and 3 indicate that this value is significantly different ($P < 0.05$) from the corresponding value in row 1, 2 or 3, respectively. The superscript 4 indicates that this value is significantly different ($P < 0.05$) from the corresponding value in the recovering group.

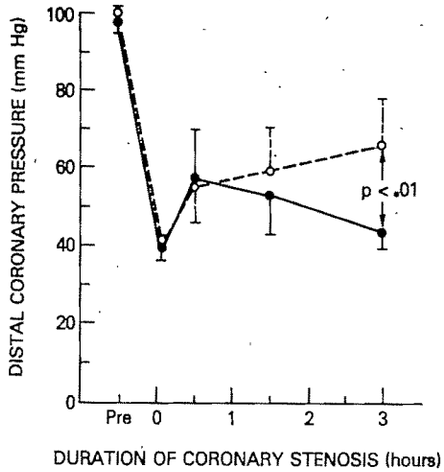


FIGURE 2. Changes in distal coronary pressure in the infarcting group **(solid line)** and the recovering group **(dotted line)** during 3 hours of stenosis. Pre = before stenosis.

Later sequelae of stenosis: The deteriorating condition of animals in the infarcting subgroup was first revealed by a decrease in distal coronary pressure after the initial increase, whereas animals in the recovering subgroup had progressively increasing distal coronary pressures (Fig. 2, Table III). In the infarcting subgroup, aortic flow had to be significantly reduced to prevent an increase in left atrial pressure. In one animal, palpable and visible mitral regurgitation developed at 3 hours, causing an elevation of left atrial pressure in that animal to 20 mm Hg in spite of a reduction in aortic flow to 1.4 liters/min. This single very high value for left atrial pressure elevated the mean value for left atrial pressure in the infarcting animals at 3 hours to 10.8 ± 2.5 mm Hg. If this high value is omitted, the mean value in the remaining four animals was 8.5 ± 1.2. With this single exception, control of left atrial pressure, even in the infarcting group, was quite good: the average change in pressure between any two microsphere injections in the infarcting group was 1.1 ± 0.2 mm Hg (mean of the absolute values of changes) with a range of 3 mm Hg.

Regional blood flow in the circumflex region was less in the infarcting than in the recovering group whereas left anterior descending regional flow was greater in the infarcting than in the recovering group (Fig. 3). Indeed, flow to the region of the left circumflex artery in the recovering group increased to levels similar to those in the region of the left anterior descending coronary artery. Although transmural circumflex arterial regional flow decreased with time in the infarcting group, this decrease was primarily in the deeper layers, and epicardial flow tended to increase or remain constant in a manner similar to that in the recovering group (Fig. 4). The transmural distribution of flow between 30 minutes and 3 hours was dramatically altered in the infarcting group compared with the recovering group (Table IV).

S-T elevation was relatively constant for the final 2 1/2 hours of stenosis in the recovering group, but endocardial S-T elevation tended to increase over this same interval in the infarcting group (Table III). Epicardial S-T elevation in the infarcting group became either strongly positive (more than 1.5 mv/electrode) in three dogs or strongly negative (−0.8 mv and −1.8 mv/electrode) in two dogs. The three dogs that manifested epicardial S-T elevation were found to have decreases in epicardial regional flow during the final 2 1/2 hours of stenosis, whereas the two that manifested negative epicardial S-T segments had increases in epicardial regional flow.

Temporal change in pressure-flow relations in ischemic region: The change in epicardial flow in the infarcting group between 30 and 180 minutes was significantly different ($P < 0.05$) from the simultaneous change in endocardial flow (Fig. 4). This suggests a time-related increase in vascular resistance in the more ischemic subendocardium. A second method of analysis proves such an increase. The pressure-flow relation between effective coronary pressure (coronary pressure minus right atrial pressure) and endocardial flow was computed using least-squares linear regression analysis for the 32 points representing pressure and endocardial flow in the recovering group and the 5 and 30 minute determinations in the infarcting group. Regional flow measurements were normalized by dividing by the average of 5, 30, 90 and 180 minute determinations of transmural anterior descending coronary arterial flow. A second linear regression was per-

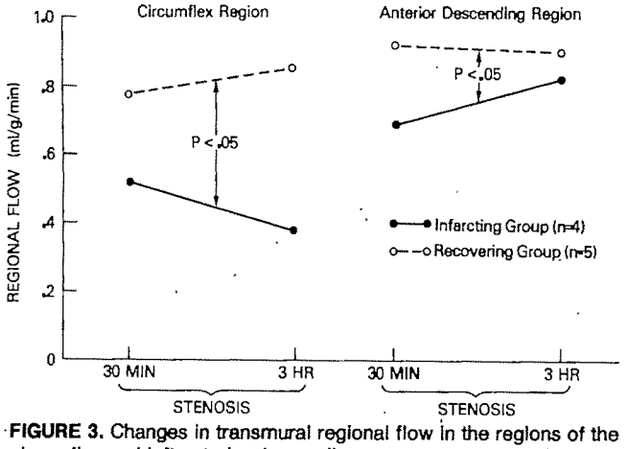


FIGURE 3. Changes in transmural regional flow in the regions of the circumflex and left anterior descending coronary arteries in both the infarcting and recovering groups during the final 2 1/2 hours of stenosis.

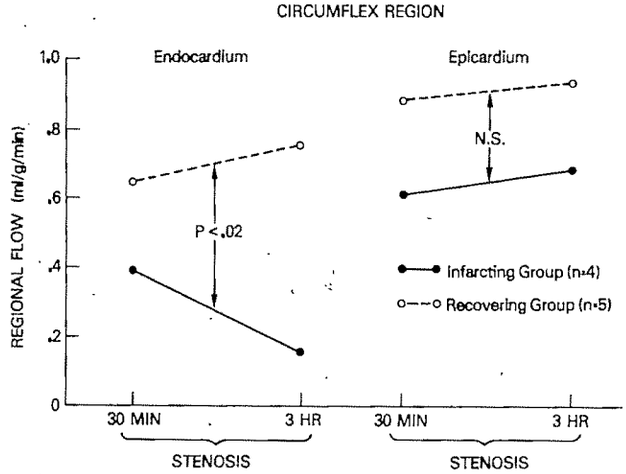


FIGURE 4. Endocardial and epicardial flow in the region of the circumflex coronary artery in the infarcting and recovering groups during the final 2 1/2 hours of stenosis.

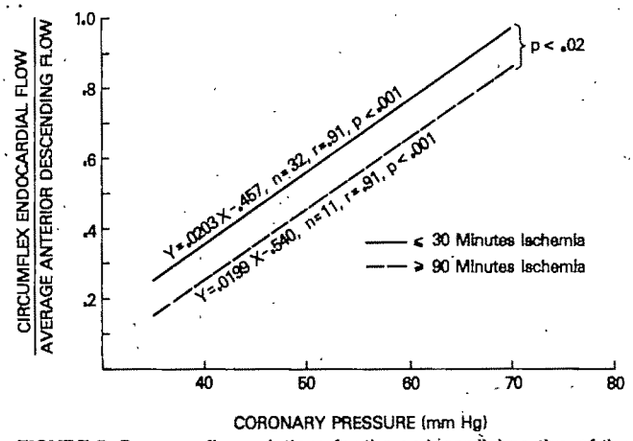


FIGURE 5. Pressure-flow relations for the endocardial portion of the region of the circumflex coronary artery determined from myocardium subjected to less than 30 minutes **(solid line)** and more than 90 minutes **(dashed line)** of ischemia.

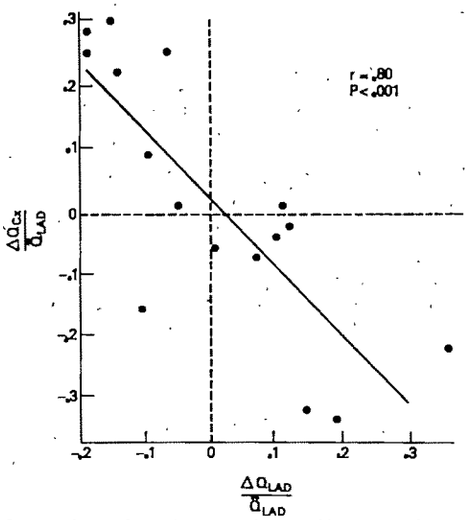


FIGURE 6. A reciprocal relation was observed between changes in flow in the area of the left anterior descending coronary artery (ΔQ_{LAD}) and changes in flow in the area of the circumflex artery (ΔQ_{Cx}) in the infarcting group in this preparation. Changes in flow were normalized by dividing by the average of the 5, 30, 90 and 180 minute determinations of flow in the area of the left anterior descending coronary artery in each animal ($\overline{Q}_{LAD}$).

formed using the 11 measurements of flow and pressure made in the infarcting group after 90 or 180 minutes of stenosis. Both regression lines fit the experimental points very well ($r = 0.91$) (Fig. 5). Statistical comparison of the two lines revealed that the slopes of the lines were similar but the intercepts significantly different ($P < 0.02$).[11] Thus, ischemia of at least 90 minutes' duration seems to have caused a shift in endocardial pressure-flow relations so that, for a given coronary pressure, flow is reduced; that is, subendocardial vascular resistance has increased.

Relation of flow in the nonischemic area to flow in the ischemic area: The decrease in distal coronary pressure and flow in the ischemic area observed in the infarcting group was perplexing. A search for the cause of this observation led to the discovery of a reciprocal relation between changes in flow to the region of the left anterior descending coronary artery (ΔQ_{LAD}) and changes in flow to the region of the left circumflex artery (ΔQ_{Cx}). The incidence of positive or negative circumflex regional flow or changes in coronary pressure associated with increases or decreases in flow in the left anterior descending coronary artery is presented in Table V. Applying the chi-square test for a 2 by 2 table, changes in left anterior descending regional arterial flow were reciprocally related to changes in both circumflex area flow and distal coronary pressure in the infarcting group ($P < 0.025$). No such significant relation was identified in the recovering dogs. The linearity of this relation was examined using linear regression analysis. Changes in flow were normalized by dividing by the average of the 5, 30, 90 and 180 minute values for transmural anterior descending coronary arterial flow in each dog ($\overline{Q}_{LAD}$). For changes in circumflex area flow (Fig. 6):

$$\frac{\Delta Q_{Cx}}{\overline{Q}_{LAD}} = -1.08\,\frac{\Delta Q_{LAD}}{\overline{Q}_{LAD}} + 0.3$$

($r = 0.80$, no. = 16, $P < 0.001$)

For changes in distal coronary pressures (Fig. 7)

$$\Delta CP = -63.9\,\frac{\Delta Q_{LAD}}{\overline{Q}_{LAD}} + 1.3$$

$r = 0.79$, no. = 16, $P < 0.001$)

Discussion

Severe myocardial ischemia is not a stable situation. Either perfusion is restored or necrosis occurs. This investigation seeks to explore the intracardiac sequelae of ischemia that determine tissue survival or necrosis. In hemodynamically isolated hearts, the evolution of myocardial ischemia was observed for 3 hours in two situations: (1) constant distal circumflex arterial pressure, (2) constant proximal circumflex stenosis.

TABLE V

Relation of Changes in Left Anterior Descending Coronary Arterial Flow to Changes in Circumflex Area Flow and Distal Coronary Pressure

	Left Anterior Descending Coronary Arterial Flow	Change in Circumflex Area Flow		Change in Distal Coronary Pressure	
		Increased	Decreased	Increased	Decreased
Infarcting group	Increased	1	7	1	7
	Decreased	7	1	7	1
Recovering group	Increased	4	1	3	2
	Decreased	7	3	10	0

Constant distal circumflex arterial pressure cannot be compared with naturally occurring coronary stenosis. With alteration of inflow through the stenosis to maintain a constant pressure in the ischemic areas, there is a tendency to compensate for changes in the other source of inflow, collateral flow. Thus, collateral changes and changes in the ischemic vascular bed can be separated, and one can focus on changes in vascular resistance in the ischemic area as a mechanism for determining cell death or survival.

Changes in resistance during ischemia and reperfusion: In this study, resistance more than doubled in the severely ischemic subendocardium during the 3 hour observation period. Small changes in resistance were observed in the less ischemic subepicardium, and resistance did not change in the nonischemic myocardium. Severe ischemia has been shown to alter a vascular system sufficiently to impair reperfusion of that system, an alteration that has been called the "no reflow phenomenon."[12,13] The increased resistance has been attributed to cell swelling and compression of vascular channels.[14–16] In the heart, impairment of reperfusion has been demonstrated after 2 to 3 hours of severe ischemia in several animal models, and subendocardial flow is particularly compromised upon reperfusion.[3–5] But it is not clear in these models that the change in resistance is caused by ischemia rather than by reperfusion. Actual extension of infarction, usually associated with hemorrhage, has been documented with reperfusion.[17–19] Reperfusion after as little as 40 minutes of occlusion causes very rapid water accumulation and electrolyte alterations in transiently ischemic cells compared with myocardium subjected to permanent ischemia.[20,21] It is therefore important to distinguish between permanently ischemic myocardium and reperfused myocardium and to point out that the changes in resistance documented in our study occurred during "permanent" (uninterrupted) ischemia. Reperfusion in this model led to normal flow in all layers. This does not imply that the coronary circulation returned to normal upon reperfusion: The dilatory capacity of the system may have been impaired although resting flow was normal. But it does imply that the changes in resistance caused by partial occlusion in our study were either less severe or more reversible than the changes found by others after complete occlusion with reperfusion.

Two factors may have influenced the results of this portion of our study. First, there was a significant 3 mm Hg increase in left atrial pressure during the 3 hours of ischemia. This change is small compared with the change that has been shown to alter the endocardial/epicardial flow ratio during ischemia,[22] but it may have had some effect. Second, collateral channels may exist that permit blood flow but not microsphere flow. Schaper[2] has estimated that the average size of collateral channels in the dog is 40 μ, large enough for microsphere flow. Studies with complete occlusion have demonstrated that microspheres can traverse collateral vessels after acute canine coronary occlusion.[23–25] But one cannot guarantee that the microsphere technique

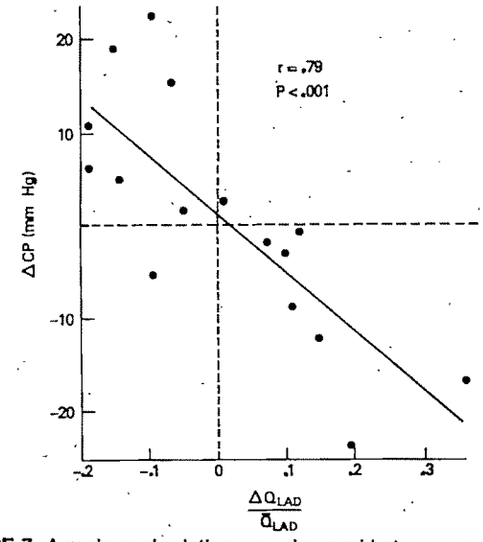


FIGURE 7. A reciprocal relation was observed between normalized changes in flow in the area of the left anterior descending coronary artery ($\Delta Q_{LAD}/Q_{LAD}$) and the changes in distal coronary pressure (ΔCP) in the infarcting group in this preparation.

does not underestimate collateral flow after acute coronary stenosis. One must make the important assumption, for the purposes of this discussion, that collateral flow contains approximately the same concentration of microspheres as does flow through the stenosis.

Implications of a time-related regional increase in resistance in an ischemic coronary circulation: The implications are profound. If ischemia increases local resistance, then ischemia leads to further ischemia, and a powerful vicious cycle is initiated. Equally important, increased resistance in a subregion of an ischemic area will tend to augment flow to the remainder of that area. Consider the schematic representation of the coronary system shown in Figure 8. Assume that aortic and right atrial pressure and collateral and proximal circumflex resistance ($R_S + R_{Cx}$) are constant. If resistance in the more ischemic subendocardium (r_{CxN}) increases with time whereas resistance in the less ischemic subepicardium (r_{CxP}) is unchanged, then total distal circumflex resistance will increase, distal circumflex pressure will increase and flow to the less ischemic subepicardium will increase whereas flow to the more ischemic subendocardium will decrease. The regional pressure-flow relation of the different myocardial layers are such that very small changes in distal coronary pressure may cause very large changes in flow to the outer layers. An ischemia-mediated increase in resistance may cause a demarcation of this ischemic area into two subregions, one with progressively decreasing and one with gradually increasing flow. Necrosis of the more ischemic portions of a hypoperfused region may contribute to salvage of jeopardized muscle in the less ischemic subregions. Because coronary hypoperfusion is heterogeneous, one should not expect the simple slicing maneuver used in our study to follow the lines of possible demarcation. For this reason, analysis of flow

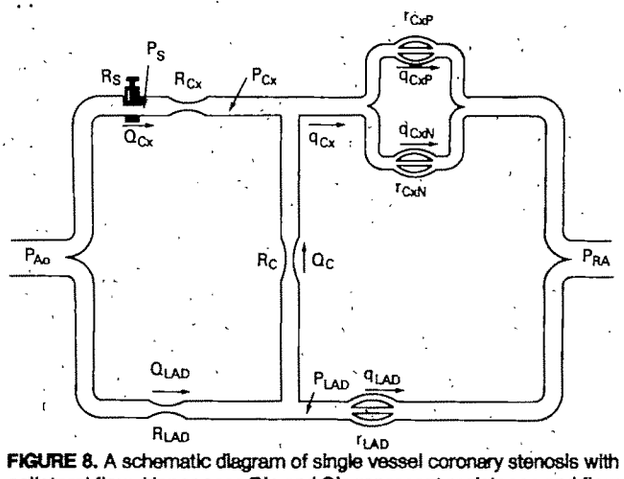


FIGURE 8. A schematic diagram of single vessel coronary stenosis with collateral flow. Upper case R's and Q's represent resistance and flow levels proximal to the collateral network and lower case r's and q's represent resistance and flow levels distal to the collateral network. Subscripts S, C, LAD and Cx denote the imposed stenosis and collateral, left anterior descending and circumflex vessels, respectively. CxN refers to the endocardial portion of the distal circumflex vascular bed and CxP refers to the epicardial portion of the distal circumflex vasculature. P_{Ao} and P_{RA} are pressures in the aorta and right atrium. P_{LAD} is a hypothetical pressure representing the average pressure at the junction of the collateral system with the left anterior descending system. P_{Cx} is a similar pressure in the circumflex system. P_S is the pressure in the circumflex system just distal to the imposed stenosis. P_S is the pressure usually measured in experimental animals and may or may not equal P_{Cx}. Reproduced from Guyton and Daggett[6] with permission.

changes in the middle myocardial layers in our model does not demonstrate demarcation nor should such a demonstration be expected.

The existence of the ischemia-mediated mechanism of demarcation is suggested by data from other studies. Rees and Redding[26] found no flow in the center of a 3 day old canine infarct; avascular areas after infarction are demonstrable on angiography[2] or at autopsy[27]; and intramural coronary vessels within an infarct undergo coagulation necrosis.[27] There is abundant evidence[1,2] that total collateral flow does not decrease with time. Therefore, if the necrotic subregion becomes avascular and total ischemic area flow does not decrease, flow per unit of mass to the residual surviving myocardium must increase with time. This ischemia-mediated demarcation may explain the fact that in areas in which infarction is not massive, cell death and survival occur, not in scattered cells, but in circumscribed foci.[27-29]

Collateral vascular changes influencing regional ischemia: The second situation studied in our investigation, an attempted constant proximal coronary stenosis, allows vascular changes in collateral vessels as well as in ischemic areas to influence regional ischemia. Analysis of the results in this section of the study is necessarily complex. Again, the aforementioned assumption that the microsphere technique accurately estimates collateral flow is utilized. A second assumption is also important: that the imposed stenosis is in fact nearly constant. The mechanical structure of the constricting device imposes a constant cross-sectional area upon the external size of the circumflex artery, but the internal diameter might be increased by stress-relaxation or decreased by swelling of the cells. An attempt was made to measure flow in the circumflex artery in this preparation, but the flowmeter caused undesirable distortion of the artery and was too inaccurate to be valid at the low flow levels necessary to create ischemia (about 3 to 10 ml/min). Both of these assumptions are utilized in the following discussion.

During the first 30 minutes after stenosis, both distal coronary pressure and circumflex regional flow increased (Table IV, Fig. 2). These two observations imply that collateral flow also increased. In this preparation, the circumflex area receives flow both across the stenosis and from collateral channels. Consider again the schematic representation of this preparation shown in Figure 8. If distal coronary pressure (P_S) increases, then the pressure gradient across the stenosis ($P_{Ao} - P_S$) must decrease (because P_{Ao} is constant) and flow across the stenosis (Q_{Cx}) must decrease. Because collateral flow (Q_C) is equal to circumflex area flow (q_{Cx}) minus flow across the stenosis, a concomitant increase in both q_{Cx} and P_S necessarily implies an increase in collateral flow ($=q_{Cx} - Q_{Cx}$). Similarly, and of importance later, a concomitant decrease in both q_{Cx} and P_{Cx} implies a decrease in collateral flow. Collateral flow, then, increases in this preparation during the first 30 minutes after stenosis.

The preference of increased collateral flow in this first 30 minutes for the endocardium could have been predicted from consideration of regional pressure-flow relations. Because epicardial flow is near normal at 5 minutes, autoregulation will tend to prevent any increase in epicardial flow as distal coronary pressure increases. Epicardial resistance will tend to increase. However, the endocardial vasculature seems to be maximally dilated over a pressure range of 35 to 70 mm Hg in this preparation. As distal coronary pressure increases, flow to the endocardium increases (Table IV) and calculated endocardial vascular resistance actually decreases ($P < 0.01$). Resistance in these vessels with minimal muscle tone (minimal because of ischemia) is a function of internal distending pressure and external compression forces. As internal pressure increases (Fig. 2), one would expect the observed decrease in resistance.[6]

Differences between infarcting and recovering groups: After 30 minutes, the evolution of ischemia in the two subgroups began to be divergent. In the recovering group, circumflex area flow and distal coronary pressure slowly increased, left anterior descending coronary arterial regional flow remained constant and ventricular function was very stable. In the infarcting group, circumflex area flow and distal coronary pressure decreased, left anterior descending regional flow increased and ventricular function gradually deteriorated. This divergence is a puzzle whose solution would do much to clarify the feedback mechanisms in myocardial infarction.

The initial differences between the two groups are important (Table I). Aortic flow was 15 percent greater and left atrial pressure 1 mm Hg less in the recovering group, but these differences were not significant. Aortic pressure (as reflected by coronary pressure) was initially

3 mm Hg greater in the recovering group, a small but significant difference. The major observed difference occurred in dP/dt, which was nearly 50 percent greater in the recovering group. This implies that, with approximately the same work output, the recovering group had a higher level of oxygen consumption per minute. As stenosis was imposed, the end point utilized was epicardial S-T segment elevation, that is, transmural ischemia. It is easy to understand that transmural ischemia occurred at higher levels of circumflex area flow in the animals with greater oxygen consumption. It also occurred at slightly greater circumflex pressure in the recovering group (difference not significant). The experimental technique thus led to greater circumflex area flow in the hearts with greater estimated oxygen consumption.

At 30 minutes, the two groups still had very similar values for aortic flow, left atrial pressure and circumflex coronary arterial pressure, whereas dP/dt and ischemic area flow were still greater in the recovering group (Tables III and IV). Subendocardial S-T elevation persisted in the recovering group but was essentially abolished at 30 minutes in the infarcting group. By S-T segment criteria, the discrepancy between perfusion and demand was greater in the recovering group at 30 minutes, although the flow level was lower in the infarcting group. Perhaps this implies that the perfusion required to maintain cell integrity is not identical to that required to prevent injury current. The hearts with lower flow levels and minimal S-T segment changes at 30 minutes later deteriorated whereas those with higher flow levels, greater oxygen consumption and endocardial S-T elevation recovered. This divergence suggests that positive feedback mechanisms are operative in our model and that perfusion itself is the critical factor in these mechanisms.

Collateral flow involvement in self-propagation of ischemia: In the first section of this investigation, an ischemia-mediated increase in resistance was suggested as a positive feedback mechanism by which ischemia is self-propagating. The data from this section also reveal an ischemia-mediated increase in resistance, but a more complex analysis is required. The pressure-flow relation for the endocardial layer is represented by the top line in Figure 5. This relation is derived from 32 pressure-flow determinations in endocardial layers subjected to less than 30 minutes of ischemia. A significantly different relation was determined if data were derived only from endocardial layers subjected to greater than 90 minutes of ischemia (bottom line in Figure 5). At an effective distal coronary arterial pressure of 40 mm Hg, for example, one would expect a normalized endocardial flow value of 0.36 in nonischemic myocardium but a flow value of 0.26 if ischemia had been present for more than 90 minutes. In this example, an ischemia-mediated increase in resistance would cause a 28 percent reduction in expected flow. This shift in the endocardial pressure-flow relation is evidence for a substantial role of an ischemia-mediated increase in resistance in the reduction of endocardial flow observed in these animals. If the increase in resistance were the only feedback mechanism operative in the infarcting group, one would expect a gradual increase in distal coronary pressure, a gradual decrease in circumflex endocardial flow and perhaps a small increase in circumflex epicardial flow. But these do not occur. A second mechanism involving collateral flow appears to be superimposed upon changes in local resistance.

In the recovering group, the concomitant increase in flow in the ischemic area and distal circumflex coronary arterial pressure implies a gradual increase in collateral flow after 30 minutes (see preceding discussion on collateral flow). In the infarcting group, the concomitant decrease in flow and pressure implies a decrease in collateral flow after 30 minutes. These observations suggest that collateral flow is indeed involved in the self-propagation of ischemia. An alternative explanation for these changes in flow and pressure involves rejecting the assumption that the stenosis is nearly constant. If in the recovering group the proximal stenosis gradually diminishes and if in the infarcting group it first decreases then increases after 30 minutes, these results might be obtained without invoking changes in collateral flow. But this alternative explanation requires the unlikely assumption that the stenosis behaves differently in the two groups.

Reciprocal relation between left anterior descending coronary arterial flow and collateral flow: Collateral flow, in our model, is derived from the region of the left anterior descending coronary artery. In the infarcting group, changes in left anterior descending regional flow are reciprocally related to changes in distal coronary pressure and flow in the region of the left circumflex artery; that is, if flow in the left anterior descending area increased, then both distal coronary pressure and flow in the circumflex arterial area decreased. Similarly, a decrease in left anterior descending coronary arterial flow was associated with an increase in both distal coronary pressure and flow in the circumflex arterial area. As discussed earlier, a concomitant increase in both distal coronary pressure and circumflex regional flow implies an increase in collateral flow and a decrease in both implies a decrease in collateral flow. Changes in flow in the region of the left anterior descending coronary artery were thus reciprocally related to changes in collateral flow in the infarcting group.

The absence of such a reciprocal relation in the recovering group was not surprising. Flameng et al.[25] have emphasized that dilatory capacity in the recipient area is very important when considering potential steal mechanisms. The same stimulus that acts to increase or decrease flow in the donor area will similarly tend to increase or decrease flow in the recipient area if dilatory capacity is available. Dilatory capacity in this preparation persists in the epicardium at distal coronary pressures as low as 45 mm Hg and increases as distal coronary pressure increases.[8a] Clearly, the recipient area of the recovering group had more dilatory capacity (coronary pressure was greater at 90 and 180 minutes) than did the recipient area of the infarcting group and

one would expect that a steal mechanism would be more difficult to demonstrate in the recovering group.

Coronary steal mechanism: Does the existence of a reciprocal relation between donor area flow and collateral flow necessarily imply that a coronary steal mechanism is operative in this preparation? Consideration of the hemodynamics of coronary occlusion and analysis of other investigations suggest that coronary steal is possible.

Using the diagram of the coronary circulation in Figure 8, consider the situation of acute proximal circumflex occlusion ($R_a = \infty$) in the normal dog. Severe ischemia in this situation[2,26] may be presumed to cause maximal autoregulatory dilation of circumflex area vasculature. Collateral vessels are small, averaging 40 μ in diameter, and are usually considered to act as passively distensible conduits.[1,2] Collateral flow will be constant if pressure in the distal left anterior descending coronary artery (P_{LAD}), right atrial pressure (P_{RA}), collateral resistance (R_C) and distal circumflex area resistance (r_{Cx}) remain constant. But suppose P_{LAD} decreases. Collateral resistance may increase since transmural pressure in the collateral system will decrease and distal circumflex resistance will increase because transmural pressure in that vasculature will also decrease. Collateral flow will then be reduced by the decrease in P_{LAD}, the increase in collateral resistance and the increase in distal circumflex resistance. The effect of an alteration in pressure in the distal left anterior descending coronary artery (P_{LAD}) on collateral flow is therefore magnified by these resistance considerations.

The pressure at the origin of collateral vessels (P_{LAD}) is a critical determinant of collateral flow and is the crux of any possible steal mechanism. If changes in flow to the donor area (q_{LAD}) are to influence collateral flow, then resistance in the distal left anterior descending coronary artery (r_{LAD}) must not be so much greater than resistance in the proximal left anterior descending coronary artery (R_{LAD}) that changes in r_{LAD} cause negligible changes in P_{LAD}. Winbury et al.[30] estimated vascular resistance between the aorta and a small (0.5 mm) coronary artery. They found that this proximal resistance was about 5 percent of total coronary vascular resistance under resting conditions and increased to 20 percent of total resistance during reactive hyperemia. Because the proximal resistance applicable in our model is between the aorta and 40 μ vessels rather than 500 μ vessels, proximal resistance (R_{LAD}) is larger than that considered by Winbury et al. and is not negligible relative to distal resistance (r_{LAD}), particularly when the latter decreases in large flow situations. One would predict, then, that P_{LAD} and collateral flow can be altered by changes in distal resistance.

Kattus and Gregg[31] used retrograde flow to examine the participation of collateral vessels in reactive hyperemia. During reactive hyperemia in the donor area vasculature, they found that retrograde flow collected from the recipient area was diminished in 21 of 24 dogs. They concluded that reactive hyperemia does not dilate collateral vessels. But their data suggest more than this conclusion; they suggest that conditions compatible with coronary steal may exist even in the absence of occlusive disease involving the donor artery, if flow is greatly increased.

Studies of collateral flow during acute myocardial ischemia in dogs have been conducted using pharmacologic agents to increase donor area flow. After total coronary occlusion, dipyridamole caused no increase in retrograde flow from the recipient area at a time when donor area flow was greatly increased.[7] Other investigators studying circumflex stenosis found that dipyridamole increased donor area flow and decreased recipient area flow, but this study was complicated by a decrease in aortic pressure after administration of dipyridamole.[8] Isoproterenol, administered acutely and 1 week after acute coronary occlusion, caused an increase in regional flow in the donor area (as studied with color-coded microspheres) and a decrease in recipient area flow, but the effects of the drug on systemic hemodynamics were not reported.[32] Thus, coronary steal of the type suggested by our study has been suggested but not conclusively demonstrated using pharmacologic agents to alter donor area flow. Drugs, however, tend to alter both proximal (R_{LAD}) and distal (r_{LAD}) resistance, whereas a metabolically-mediated increase in donor area flow may more specifically alter distal resistance.[6]

Alternative explanations for reciprocal relations: Coronary steal, although theoretically possible, has so little solid support from other investigations without hemodynamic control that one must seek alternative explanations for the reciprocal relations demonstrated in our study. Any such alternatives are difficult to defend. A primary time-related increase in distal vascular resistance in the recipient area (leading to increased recipient area ischemia and increased work output from the donor area) should have been associated with an increase in distal coronary pressure. A primary time-related increase in collateral resistance could explain the relation observed, but the collateral vasomotor state seems to be unresponsive to pharmacologic intervention early after coronary occlusion,[1] and the location of canine collateral vessels in the epicardium,[2] which was only minimally ischemic in our preparation, makes an ischemia-mediated increase in collateral resistance unlikely. A direct effect of changes in left atrial pressure is another possible mechanism. If increased left atrial pressure (as ventricular function deteriorates after ischemia) causes increased flow in the region of the left anterior descending coronary artery and decreased collateral flow, then the direct effect of changes in left atrial pressure might explain the donor area flow-collateral flow relation observed in the infarcting group. But chi-square analysis does not reveal a statistically significant relation between directional changes in left atrial pressure and such changes in left anterior descending or circumflex regional flow or distal coronary pressure. Moreover, if one omits the single instance in which left atrial pressure could not be controlled (see Results) the changes in left atrial pressure were very small (averaging 1 mm Hg, range 0 to 3 mm Hg) compared with the magnitude of the change on left atrial pressure that has been shown to affect collateral flow.[22]

Competitive redistribution of coronary flow: Feedback mechanism: Coronary steal usually refers to a decrease in collateral flow in association with an increase in donor area flow. A second type of steal, subendocardial to subepicardial redistribution of flow

distal to a stenosis, has been described[25] and may be sufficient to lead to selective subendocardial infarction. A third form of redistribution is probable when two stenoses are in series, for example, a left main coronary stenosis and an obtuse marginal stenosis. If oxygen demand increases, total flow in the left main coronary artery will increase, the pressure gradient across the stenosis of this artery will increase and a smaller pressure gradient will be available to force flow through the more distal obtuse marginal stenosis. "Competitive redistribution of flow," defined as any impairment (relative or absolute) of local coronary flow in response to an increase in coronary flow in another region, is a broader term than "coronary steal" and includes all three of these mechanisms. Of the mechanisms, endocardial to epicardial redistribution seems well established,[25] donor area "steal" of collateral flow is suggested by our investigation and other studies without hemodynamic control[7,8,32] and redistribution involving two stenoses in series has not been studied.

An important feature of competitive redistribution is the potential positive feedback mechanism that is implied. The steps in this feedback mechanism are (1) decreased work output from the ischemic area; (2) increased demand for work from the nonischemic area; (3) increased flow to the nonischemic area; (4) decreased collateral flow to the ischemic area; (5) further decreased work output from the ischemic area, and so forth. Compensation for loss of contraction in an ischemic area by increased shortening in the nonischemic area has been demonstrated after acute coronary occlusion.[33,34] In our preparation competitive redistribution was associated with moderate deterioration of ventricular function in the infarcting group (Table III).

But competitive redistribution is not undirectional. A decrease in myocardial oxygen demand (for example, with sedation and bed rest) may decrease coronary flow in the donor area and thus lead to an increase in ischemic area flow that in turn leads to increased work output from the ischemic area and decreased demand for work from the donor area, and so forth. Indeed, the effect of any alteration in myocardial oxygen demand would be magnified by a feedback mechanism involving competitive redistribution because increased total oxygen demand tends to retard flow in the ischemic area and decreased total oxygen demand tends to augment it.

Clinical implications: Two positive feedback mechanisms seem to be operative in our preparation: an ischemia-mediated local increase in resistance and competitive redistribution of coronary flow. But the functional significance of such mechanisms in human infarction is difficult to estimate. There is evidence that subendocardial and even transmural infarction may occur in man without an acute increase in proximal coronary resistance.[35,36] This observation suggests that vicious cycles of ischemia causing more ischemia may be initiated by a temporary increase in oxygen demand in the presence of a severe but stable limitation of oxygen supply. Positive feedback systems similar to those suggested by our investigation not only may be operative in this type of infarction but also may be the primary mechanisms causing the discrepancy between oxygen supply and demand that leads to myocardial necrosis.

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Wenckebach Atrioventricular Block (Mobitz Type I) In Children and Adolescents

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Mobitz type I atrioventricular block in children, adolescents and young adults without overt heart disease or drug intoxication has been considered less significant than Mobitz type II block. In highly trained athletes and some nonathletes it has been presumed to be a benign manifestation of heightened vagal tone. Experience with 16 young patients, 6 female and 10 male, tends to alter the concept of benignity. Known onset of Wenckebach and varying first degree block was between 6 months and 17 years of age. Of eight patients followed up for 5 to 18 years, five have fixed complete heart block and three first degree block. Of eight followed up for 1 to 4 years, two have fixed complete heart block and the others varying first, second and third degree block. Two have required a pacemaker implant. On intracardiac electrography performed in seven patients, four manifested during sinus rhythm a Wenckebach response to atrial pacing at abnormally slow rates; in addition, the His bundle electrograms showed A-H delay in one patient, H-V delay in two patients and delay in both intervals in one patient. Of three patients studied during complete heart block all manifested A-H block and one also H-V prolongation. The occurrence of Wenckebach block in 7 of 16 children and adolescents before the development of fixed complete heart block suggests that such block is probably more common than heretofore recognized and may be a phase in the natural history of the development of idiopathic heart block. It often represents significant disease of the cardiac conduction system, which may be progressive, and it has a guarded prognosis.

Wenckebach[1] in 1899 described a form of conduction disturbance manifested by a progressive lengthening of the *a-c* interval of the jugular pulse terminating in a dropped *c* wave. Twenty-five years later, after introduction of the electrocardiogram, Mobitz[2] demonstrated that this conduction disturbance represented a progressive prolongation of the P-R interval until the occurrence of a blocked ventricular response, that is, Mobitz type I or Wenckebach second degree atrioventricular (A-V) heart block. In the Mobitz type II second degree block the P-R interval is constant prior to the blocked ventricular response; often there is also prolonged intraventricular conduction.

Wenckebach and Winterberg[3] later elaborated further on the electrocardiographic details of the arrhythmia and characterized it as an intermittent dropping of a ventricular beat associated with (1) progressive lengthening of the P-R interval, with the largest increment occurring between the first and second conducted beats; (2) progressive decrease in R-R intervals; and (3) a pause produced by the nonconducted P wave equal to the difference between the last P-R interval before the pause and the first P-R interval after the pause subtracted from twice the P-P interval.

Although these criteria define "typical Wenckebach periodicity," Wenckebach suggested that variations were frequent. Subsequently others have also demonstrated departures from the typical pattern in-

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cluding dropped atrial beats,[4] Wenckebach periods of alternate beats[5] and the occurrence of the greatest increment in the P-R interval of the last conducted beat.[6] In a recent study[6] so-called atypical periodicity was shown to be more common than typical periodicity.

The development of intracardiac electrography has allowed more precise localization of the sites of A-V condition delay or block. Most studies have been performed in adults. In general, the prognosis has been considered benign in type I Wenckebach block,[7] where the conduction delay is typically localized to the area of the A-V node (A-H prolongation)[8,9]; it has been thought more ominous[7] for the development of complete heart block in type II in which the delay usually

TABLE I

Sixteen Cases of Wenckebach Periodicity

Case no.	Sex	Initial Documented Arrhythmia: Age (yr)	Initial Documented Arrhythmia: Type	Course	Last Known Arrhythmia: Age (yr)	Last Known Arrhythmia: Type	Remarks
				A. Group 1: 5 to 18 Years of Follow-Up			
1	F	5	1° (P-R 0.32); 2:1; Wenckebach	Age 6: CHB; thereafter permanent CHB	23	CHB (VR 50/min)	No symptoms; on exercise, VR 70/min
2	M	7	1° (P-R 0.25)	Age 15:1° (P-R 0.45). Age 16–18:1° (P-R 0.28), Wenckebach	24	1° (P-R 0.28) (VR 75/min)	No symptoms; on exercise, VR 150/min, P-R 0.18
3	F	6	CHB	Age 7–12:1° (P-R 0.22), Wenckebach; thereafter permanent CHB	20	CHB (VR 48/min)	No symptoms; on exercise, VR 60/min
4	M	7	1° (P-R 0.36); Wenckebach	Age 12:CHB; thereafter permanent CHB	20	CHB (VR 32/min)	No symptoms; on exercise, VR 42/min
5	F	3	Wenckebach	Age 7:1° (P-R 0.21), Wenckebach. Age 8:1° (P-R 0.21). Age 10:1° (P-R 0.21), Wenckebach, CHB	16	CHB (VR 50/min), multifocal PVCs	Recurrent dizziness; on exercise, VR 75/min
6	M	7	1° (P-R 0.28)	Age 11:1° (P-R 0.32). Age 13:1°, Wenckebach	14	1° (P-R 0.22) (VR 60/min)	No symptoms; on exercise, VR 100/min, P-R 0.14
7	M	1/2	Wenckebach	Age 14 mo:1° (P-R 0.24). Age 3:1° (P-R 0.24), Wenckebach, CHB. Age 4:1° (P-R 0.24)	5	1° (P-R 0.26) (VR 75/min)	No symptoms
8	F	4	1° (P-R 0.24)	Wenckebach to CHB over 5 yr	9	CHB (VR 40/min), occasional junctional rhythm	No symptoms; absent IVC, persistent azygous to SVC; on exercise, junctional rhythm (120/min)
				B. Group 2: 1 to 4 Years of Follow-Up			
9	F	17	Wenckebach	Unchanged for 3 yr. Age 20:CHB	21	CHB	On exercise, Wenckebach to RSR 90/min, P-R 0.20 Age 20: syncope, paced
10	M	16	1° (P-R 0.28); Wenckebach	Age 16–18: unchanged	19	1° (P-R 0.28), Wenckebach, CHB	No symptoms
11	M	15	1° (P-R 0.28); Wenckebach; VT	CHB once, then 1° (P-R 0.24)	17	1° (P-R 0.21) (VR 80/min)	No symptoms (basketball player); on exercise, VR 100/min, P-R 0.16
12	F	17	1° (P-R 0.24); Wenckebach	1° (P-R 0.21), CHB	19	Unchanged	No symptoms; on exercise, during CHB, to RSR 70/min, P-R 0.16; during Wenckebach, to RSR 125/min, P-R 0.16
13	M	4	2:1; Wenckebach	Age 5: 2:1, Wenckebach	6	CHB (VR 42/min)	No symptoms; on exercise, during CHB, VR 75/min (CHB); during Wenckebach, no change
14	M	15	Wenckebach	Unchanged	16	Wenckebach	No symptoms (trained athelete); on exercise, RSR 100/min, P-R 0.22
15	M	10	1° (P-R 0.27); Wenckebach	Unchanged	11	1° (P-R 0.21), Wenckebach	No symptoms; on exercise, RSR 100/min, P-R 0.20
16	M	12	Sinus bradycardia, Wenckebach; nodal & ventricular escape beats	Wenckebach, CHB over 5 mo, then 1° (P-R 0.21), PVCs	13	1° (P-R 0.21) (VR 50/min)	No symptoms; on exercise, VR 140/min, P-R 0.13

CHB = complete heart block; IVC = inferior vena cava; P-R = P-R interval (sec); PVCs = premature ventricular contractions; RSR = regular sinus rhythm; SVC = superior vena cava; VR = ventricular rate; VT = ventricular tachycardia.

represents His bundle and distal conduction system disease resulting in a prolongation of the interval (H-V) from the His potential to ventricular depolarization.[8,9]

Primarily on the basis of adult studies, type I block has been assumed to be benign in children and adolescents.[10] In young highly trained athletes,[11–14] a few older trained athletes[15,16] and two nonathletic adolescents,[17] type I block was presumed an innocuous manifestation of heightened parasympathetic tone and, in the athletes, causally related to heavy physical training.[11–16] However, our experience with 16 patients, all first seen in childhood or adolescence, tends to alter this concept of benignity.

Material and Methods

Patients: The 16 patients studied were referred for evaluation of abnormal cardiac rhythms (Table I). Initial electrocardiograms showed Wenckebach periodicity in 12 and later Wenckebach periodicity in the other 4. Ten of the patients were male and six female. Type I block was documented in the youngest at age 6 months and in the oldest at age 17 years. Repeat examination and electrocardiograms at rest and after moderate exercise (vigorous sit-ups or sustained running in place) were obtained when possible at 3 to 6 month intervals. The longest follow-up period was 18 years.

Typical Wenckebach periodicity was present in 10 patients and atypical periodicity in 5 in whom the longest P-R increment was in the last conducted beat; both typical and atypical Wenckebach periodicity with dropped atrial beats occurred in one patient. In all patients the QRS complex was consistently normal.

No patient had previous or current documentation of myocarditis or a history of drug abuse. None had clinical evidence of structural heart disease. There was no family history of cardiac arrhythmias. Eight of nine patients subjected to cardiac catheterization showed no anatomic abnormality. One girl had no inferior vena cava and azygous vein return to the superior vena cava (a physiologically unimportant anomaly when unassociated with other cardiac defects).

Electrophysiologic evaluation: Seven patients underwent cardiac catheterization and His bundle studies[18] with the percutaneous sheath method.[19] Informed consent was obtained for the studies after the nature of the tests and their risks were explained to the parents and to the patients when appropriate.

The patients were sedated with morphine sulfate, 0.15 mg/kg body weight, sodium pentobarbital, 3 mg/kg, and droperidol, 0.075 mg/kg, given intramuscularly 1 hour before cardiac catheterization. Generally the catheterization and angiography were performed before the His bundle studies. The latter were performed with a multipolar catheter touching the right atrial wall just beneath the superior vena cava to monitor the high right atrial potentials and to pace the right atrium, and a tripolar catheter across the tricuspid valve to monitor the low right atrium, His bundle and right ventricular potentials. Recordings were made on an Electronics for Medicine VR6 and DR12 multichannel photographic recorder at speeds of 100 and 200 mm/sec. Several limb leads of the standard electrocardiogram were recorded simultaneously. The intracardiac electrograms were filtered to record between 30 (VR6) or 40 (DR12) and 500 hertz. Pacing rates were progressively increased in increments of 20 beats/min up to 200 beats/ min, unless A-V block developed at lower rates.

TABLE II

Degree of Heart Block on Follow-Up Study

A-V Block	Group 1 (5–18 years follow-up)	Group 2 (1–4 years follow-up)	Total
Complete	5	2	7
1°	3	2	5
Varying 1°, 2°(W), 3°	0	2	2
Wenckebach	0	1	1
Varying 1°, 2°(W)	0	1	1
Total	8	8	16

W = Wenckebach.

Three patients were studied with intravenous administration of one or several drugs. Edrophonium was given in 5 or 2.5 mg doses every 5 minutes for up to three doses. Isoproterenol was given by infusion in doses roughly adequate to double the heart rate. Atropine was given in single doses of 0.4 to 1.2 mg.

The following intervals were measured when possible: the high right atrium to low right atrium (P-A), low right atrium to His bundle (A-H reflecting A-V nodal conduction) and His potential to ventricle (H-V). Measurements were made from or to the first rapid deflection of each potential. Normal standards for children and adolescents as developed by several investigators[20–25] were utilized.

Results

Follow-Up Studies

The patients were separated into two groups. Group 1 consisted of eight patients followed up for 5 to 18 years and is thus arbitrarily considered "long-term" (Table IA). Electrophysiologic studies were performed in two. Group 2 (Table IB) consisted of eight patients followed up for 1 to 4 years and is designated "shorter term." Intracardiac electrography was performed in five of this group.

Progression of block: Conduction abnormalities were first recorded in patients in Group 1 aged 6 months to 7 years (Table IA). The first evidence of heart block was Wenckebach periodicity in four (Cases 1, 4, 5 and 7), first degree block in three (Cases 2, 6 and 8) and complete heart block in one (Case 3). The latter patient within the subsequent year showed varying Wenckebach and first degree block that persisted for the 5 years of follow-up study. All with initial first degree block manifested Wenckebach block that then persisted for various periods of time. At the time of the last follow-up examination, five patients (Cases 1, 3, 4, 5 and 8) (Table II) had fixed complete heart block. One patient (Case 5) was symptomatic but refused a recommendation for a pacemaker implantation; her condition continues unchanged. All others had no symptoms.

Of the eight patients in Group 2, all manifested Wenckebach periodicity in the initial electrocardiogram (Table IB). Four (Cases 10, 11, 12 and 15) also had first degree block and one (Case 13) had 2:1 block (one of only two in the series). Three (Cases 11, 12 and 16) have had transient or intermittent complete heart block. All currently have conduction abnormalities, two (Cases 9

TABLE III

Intracardiac Electrographic Data in Seven Patients

Case no.	Age (yr)	Resting Rhythm and Rate	A-H (msec)	H-V (msec)	Atrial Pacing
5	16	CHB (50/min)	Block	40	No effect; no effect with isoproterenol, edrophonium
8	9	CHB (40/min)	Block	35	Intermittent atrial capture
13	4	CHB (42/min)	Block	50	No effect
11	15	RSR, 1° block (70/min)	115–120	60	Wenckebach at 116/min; 2:1 and 3:1 block at 125/min
12	17	Wenckebach (60/min)	100–150	50	When paced during RSR at 70/min, Wenckebach at 88/min
14	15	RSR (60/min)	110–120	55	Wenckebach at 80/min; at 140/min with atropine; at 76/min with edrophonium
15	10	RSR, 1° block 73/min	160	40	Wenckebach at 90–100/min; at 200/min with atropine or isoproterenol

CHB = complete heart block; RSR = regular sinus rhythm.

and 13) with fixed complete heart block (Table II). All but Patient 9 have been asymptomatic.

Response to exercise: On exercise, the patients with fixed complete heart block (Cases 1, 3, 4, 5 and 13) (Table I) showed the common response with an increase in ventricular rate of 10 to 25 beats/min. One exception was Patient 8, who had a resting ventricular rate of 50/min and exhibited a junctional rhythm at a rate of 120/min on moderate exercise. One patient (Case 12) whose electrocardiogram ranged from first degree (P-R 0.24 second) to second degree (Wenckebach) and to third degree block was subjected to moderate exercise during complete block and during Wenckebach periods. During complete block sinus rhythm developed at a rate of 70/min with a P-R interval of 0.16 second. During Wenckebach periodicity the rate increased to 125/min, again with a P-R interval of 0.16 second.

Four patients (Cases 2, 6, 11 and 16) exercised while they had first degree block. All showed an increase in ventricular rate appropriate for the degree of exercise and their general physical condition. In all, the P-R interval transiently returned to normal as part of the exercise response. This was most striking in Patient 2, whose P-R interval decreased from 0.28 to 0.18 second with a doubling of the sinus rate.

The response to exercise in those with Wenckebach periodicity was more variable. Five patients (Cases 9, 11, 12, 14 and 15) manifested sinus rhythm with appropriate heart rates immediately after exercise; the P-R interval remained slightly prolonged in three (0.20, 0.22 and 0.20 second, respectively) but decreased to 0.16 second in two (Cases 11 and 12). Patients 14 and 15 showed additional conduction abnormalities on His bundle and pacing studies (Table III). One boy (Case 13) showed no change on exercise during type I block. Shortly thereafter he manifested complete heart block that has since remained fixed.

Electrophysiologic Studies

His bundle studies were performed in seven patients (Table III); three (Cases 5, 8 and 13) had complete heart block at the time of study. These patients showed A-H block commonly seen in "congenital" heart block. One patient (Case 13) also had an H-V time of 50 msec; this exceeds the maximal H-V time of 45 msec in four[20–23] of five reports of normal standards for children and adolescents.

Four patients who had intermittent Wenckebach and first degree block were studied during a period of sinus rhythm. One patient (Case 15) showed A-H delay, two patients showed H-V delay (Cases 11 and 14) and one patient (Case 12) showed both A-H and H-V delay. On atrial pacing all had Wenckebach block at pacing rates that were significantly lower than the normal standard for children of 224/min ± 45 (1 standard deviation).[25] In one (Case 15) of two patients tested the block could be "normalized" with atropine or isoproterenol.

Discussion

Incidence: Wenckebach periodicity has been considered an uncommon manifestation in children and adolescents. This is especially so in the absence of structural heart disease, intracardiac surgery, recognizable myocarditis (either nonspecific or rheumatic) or drug intoxication (mainly digitalis). Standard textbooks on pediatric cardiology have documented a few cases of children with severe congenital heart disease whose second degree block eventually progressed to fixed third degree block[26] and relatively few of children with second degree block of undeterminable origin.[26,27] Otherwise Wenckebach periodicity is attributed to rheumatic fever[28] or digitalis toxicity.[29]

Wenckebach periodicity is also uncommon in young adults. In two large electrocardiographic series, it was detected in 3 of 67,375[30] and in 1 of 19,000[31] healthy young soldiers. In the latter series, because both the Wenckebach phenomenon and first degree heart block were abolished by assumption of the erect position, A-V block was attributed to increased vagal tone and not considered indicative of organic heart disease.

Although still uncommon, the Wenckebach phenomenon reportedly occurs with greater frequency in trained athletes. It was found in a total of 7 of 4,000 athletes surveyed electrocardiographically in two studies.[11,12] The estimated incidence rate was 0.15 and 0.21 percent, respectively. Earlier reports[15,16] of the Wenckebach phenomenon in a few older persons (aged 36 to 53 years) who performed daily strenuous physical exercise suggested a causal relation between training and the phenomenon. Recently this concept was supported by Meytes et al.,[14] who demonstrated its presence in 3 of 126 leading Israeli athletes. Mobitz type I block occurred only during periods of intensive training and disappeared within a few weeks after reduction or cessation of the training program.

Natural history: Discussions of the natural history of "congenital" heart block fail to mention a relation of the Wenckebach type of second degree A-V block to the development of complete heart block.[32] Forty-six infants, children and adolescents have been under our care because of permanent complete heart block unassociated with demonstrable etiologic factors. Seven of these patients (15 percent) had documented preceding Wenckebach periodicity of varying duration. One of these is now in the series of 19 who have required permanent pacemaker implantation.[33]

It would appear that Wenckebach periodicity may be an early or intermittent phase of variable duration in the natural course of the progressive development of disease of the A-V conduction system. The detection, frequency of occurrence of Wenckebach periods and time of transition to complete heart block would then be a function of the tempo of the disease and the frequency with which electrocardiograms are obtained.

Response to exercise: Gilchrist[34] first demonstrated the difference in response to exercise between patients with type I and type II A-V block. Conduction improved in the former and deteriorated in the latter. Inasmuch as type I block commonly is the result of A-V nodal dysfunction, the vagolytic effect of exercise or atropine would be expected to improve or abolish the block. The absence of this effect in type II block occurs because the infranodal lesion is beyond most vagal influence.

We had considered reversion from type I block to sinus rhythm on exercise a reassuring clinical indication of adequate A-V conduction on stress until our experience with Patient 9. This 17 year old girl, first seen because of an asymptomatic cardiac irregularity and subsequently followed up every 4 months for 3 years, had always shown Wenckebach periodicity that on exercise invariably returned to sinus rhythm at a rate of 90/min with a P-R interval of 0.20 second. She suddenly had two severe episodes of syncope with complete heart block and junctional escape and required pacemaker implantation. Heart block has persisted during the subsequent year. At least some patients, therefore, despite normal exercise response, are at continued risk for a more serious or fatal outcome.

The other three patients (Cases 12, 14 and 15) who, during type I block, responded to exercise with a relatively normal conduction pattern have not manifested fixed third degree block. Nevertheless, all three patients had an abnormal response to atrial pacing with A-H delay (Case 15), H-V delay (Case 14) or both (Case 12), presumptively precursors to further conduction difficulties.

His bundle electrograms and atrial pacing: Although many electrophysiologic studies have been obtained in patients with heart disease and second degree block, they have been reported on in only two healthy adolescent boys with persistent type I block.[17] In both, the block was proximal to the His bundle and eliminated with exercise and atropine, thus indicating that excessive parasympathetic tone was a major cause of the A-V block. However, opinion was reserved as to the anticipated natural history of the arrhythmia.

Our studies are at variance with the concept that Wenckebach periodicity is a purely "functional" disturbance that may be of little consequence. Fixed complete heart block has developed in 7 of the 16 patients (44 percent). Electrophysiologic studies in four patients who did not have fixed third degree block have demonstrated nodal or infranodal delay, or both. Patient 14 was an athlete who had type I block on recumbency that usually disappeared on standing. Although he had a normal response to maximal stress testing with sinus rhythm and a P-R interval of 0.22 second, on electrophysiologic study there was H-V delay (H-V interval 55 msec) and, at a low rate of atrial pacing, a Wenckebach response that was not significantly improved with the administration of atropine. Patient 11 was a basketball player whose initial electrocardiogram showed Wenckebach periodicity, first degree heart block and a short run of ventricular tachycardia. He also had a normal response to maximal stress testing with sinus rhythm and a P-R interval of 0.16 second. His bundle study showed delayed H-V conduction (60 msec) and, with actual pacing, Wenckebach periodicity developed at a pacing rate of 116/min and 2:1 and 3:1 block at a rate of 125/min; these responses are probably abnormal. These findings raise significant doubt that a nonorganic functional vagal effect of training is the etiologic factor in these patients.

Mechanisms of Wenckebach block: The disturbance in A-V conduction manifested by Wenckebach periodicity has been attributed to progressive encroachment upon refractoriness of the preceding impulse,[35,36] decremental conduction[37–39] or progressive inhomogeneity of electrical wave fronts in multifibered cardiac tissue.[40,41] More recent studies[42] demonstrate the block to result from a progressive increase in maximal repolarization voltage of the transmembrane potential and a progressive decrease in the diastolic interval that, in the presence of enhanced phase four diastolic depolarization, causes the voltage level from which the potential originated to become further removed from the stimulation threshold with successive impulses of the cycle.

Whether or not the altered membrane potential in these patients is the result of a disturbance in function resulting from neurohumoral or other chemical imbalance or represents anatomic abnormality due to developmental, inflammatory or degenerative progressive involvement of the conduction system is not known. Because all patients in this series are living, histologic studies are not available.

Pathologic basis for primary heart block: In the adult, "primary" heart block has been associated with either of two pathologic processes. In Lenegre's disease[43] of the younger adult there is a sclerodegenerative process of unknown origin involving the bundle branches. Lev's disease[44] shows similar pathologic changes but is believed to occur secondary to fibrosis and calcification of the cardiac skeleton as part of an aging process. Electrocardiographic criteria for both should include development of progressive intraventricular conduction disease eventuating in complete heart block with con-

firmation of block distal to the His bundle on electrophysiologic study.[45]

The age of the patients in our series precludes the presence of the Lev type of sclerodegenerative process. Our patients also do not fit the current criteria for Lenegre's disease by virtue of age and the absence of an earlier appearance of bundle branch block. The youngest patients with presumptive Lenegre's disease have been recognized initially at age 21 years (with left bundle branch block),[45] and at age 28 years (with right bundle branch block and 2:1 A-V block).[46]

Congenital defects of the conduction system may be divided into two categories[47]: (1) absence of myocardial connection between the atrial conduction tissue and the A-V node, and (2) defects of the A-V node causing disruption of the conduction system. The latter may be either absence of the node, presumably never developmentally formed, or degeneration of a developed nodal structure. Among the 29 cases reported by Carter et al.,[47] there was no associated anomaly in only 4, 2 showing absence of the A-V node and 2 fibrous interruption of the His bundle.

Despite the frequent initial documentation of complete heart block long after infancy, in the absence of known etiologic factors it has commonly been designated "congenital" in children and adolescents. Confirmation of this origin is lacking and its isolated pathologic demonstration uncommon. It is therefore perhaps just as reasonable to postulate that these young patients, and those in our series, previously sustained a nonspecific or viral myocarditis, unrecognized from symptoms or earlier detection of electrocardiographic T wave changes, that resulted in progressive or unresolved conduction system disease.

The demonstration of Wenckebach periodicity as a frequent precursor to the development of fixed complete heart block thus tends to emphasize the potentially more serious aspect of this arrhythmia. Although the greatest incidence of death from complete heart block in children, with or without associated heart disease, occurs in the first year of life[32] and patients with congenital heart block can survive without symptoms into late adult life,[48] all such patients must be considered at constant risk of having diminished cardiac function or fatal cerebrovascular insufficiency, or both.

Conclusions

1. Wenckebach periodicity occurs not uncommonly, often transiently, as part of the natural course of disease of the A-V conduction system.
2. Recognition of its incidence and transition is a function of the varying tempo of the disease and the frequency with which electrocardiograms are obtained.
3. Response to exercise and administration of atropine and electrophysiologic studies are not useful prognostic indicators.
4. In the absence of known causative factors (significant heart disease, myocarditis, drugs) the etiology of the conduction abnormalities is not established.
5. In view of the ultimate development of complete heart block in many patients, and the demonstration of significant and often multiple conduction abnormalities in His bundle studies, Wenckebach periodicity should not be considered benign or solely a normal manifestation of transient heightened vagal tone but an abnormality that may have future serious consequences.

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Cross-Sectional Echocardiographic Features of Ebstein's Anomaly of the Tricuspid Valve

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Multicrystal real time-motion echocardiographic studies of 10 patients with Ebstein's anomaly of the tricuspid valve are reported. Eight patients also underwent hemodynamic and angiographic study. All but one of the patients had inferior and leftward displacement of the tricuspid valve. In seven patients multiple echoes were obtained from the tricuspid valve; all seven manifested elongated tricuspid valve leaflets, and in six the leaflets were thickened. Excessive excursion of the tricuspid valve was noted in five patients and a "whipping" motion seen in three. Nonspecific findings in nine patients included an increased right ventricular dimension and systolic anterior septal motion. Thus, cross-sectional echocardiography provides distinctive diagnostic findings that are specific for Ebstein's anomaly.

A wide spectrum exists in the anatomic severity of Ebstein's anomaly of the tricuspid valve. Relatively constant findings include variable redundancy of tricuspid leaflet tissue and an adherence of a portion of the posterior and, especially, the septal cusps to the right ventricular wall.[1] Among conventional single crystal echocardiographic findings observed both in patients with this anomaly and in those with other forms of right ventricular volume overload are an increase in right ventricular dimensions, paradoxical ventricular septal motion, a decrease in the E-F slope of the tricuspid valve and an abnormal closing velocity of the tricuspid valve.[2–8] More specific ultrasonic findings include an increase in tricuspid valve excursion, a delay in tricuspid valve closure relative to mitral valve closure, an abnormal anterior position of the tricuspid valve during diastole (Fig. 1) and the detection of tricuspid valve echoes with a more lateral placement of the transducer than usual.[5,9–17] Because two dimensional cross-sectional echocardiography may be expected to enhance the spatial and architectural appreciation of intracardiac malformations,[17–24] this report describes in detail our experience with this method in evaluating 10 patients with Ebstein's anomaly.

Materials and Methods

Ten patients aged 2 days to 19 years with documented Ebstein's malformation were examined with a multiple crystal echocardiographic system (multiscan) designed by Bom et al.[25] In eight patients the diagnosis and anatomic details were assessed and confirmed with standard hemodynamic and biplane cineangiographic techniques. The other two patients had typical clinical, radiographic, single crystal echocardiographic and electrocardiographic findings of Ebstein's anomaly. The qualitative cross-sectional echocardiographic findings in the 10 patients were compared with those of 100 normal infants and children to allow the development of criteria for the diagnostic separation of the two groups.

The use of the multiscan instrument has been described in detail elsewhere.[17–24] Sagittal and transverse cross-sectional images of cardiac anatomy viewed in real time on an oscilloscope were stored permanently on video tape and 8 mm motion picture film. The illustrations in this report were obtained from electrocardiographically gated Polaroid® or enlarged Kodak Super 8 mm still frames. Identification of anatomic features and structure is enhanced appreciably

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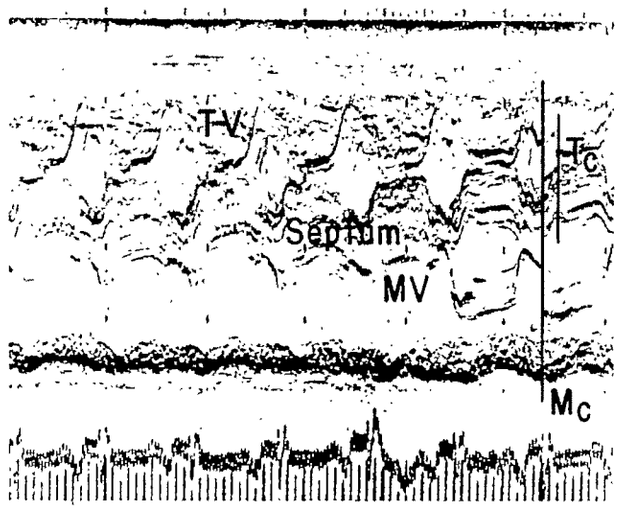


FIGURE 1. Single crystal echocardiogram from a 3 day old patient with Ebstein's anomaly. This is a deliberate sweep from the tricuspid valve (TV) to the mitral valve (MV). Both leaflets of the tricuspid valve are seen with valve closure (T_c) occurring 0.09 second after mitral valve closure (M_c). There is excessive excursion of the anterior leaflet of the tricuspid valve. Paradoxical motion of the interventricular septum is evident.

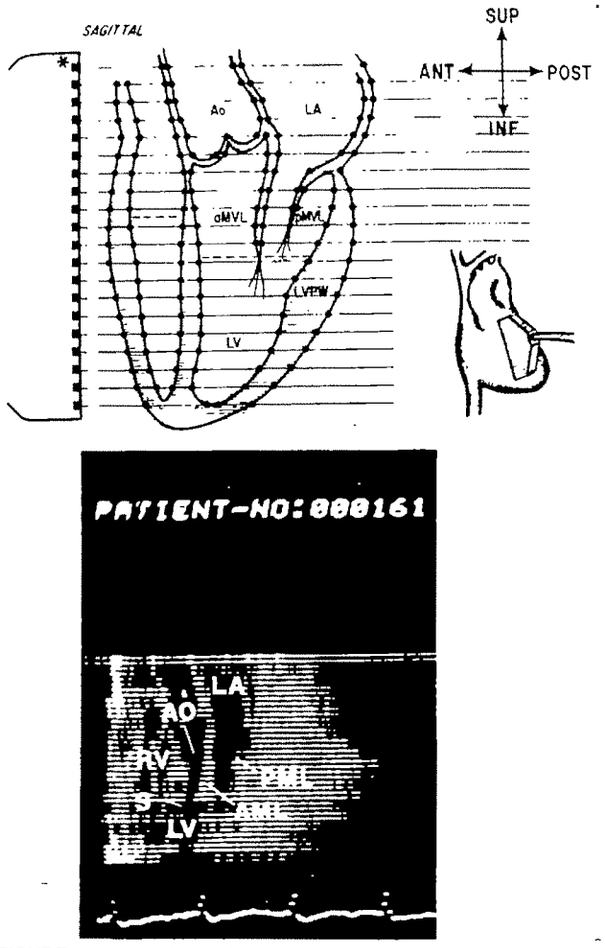


FIGURE 2. Long axis section of the normal heart with a line drawing **(upper panel)** and a multiscan Polaroid still frame **(lower panel),** showing the relation of the right and left ventricles in a sagittal plane. Transducer placement is as shown in the insert, and image orientation is demonstrated by the compass. A small portion of the normal anterior tricuspid leaflet apparatus is seen within the right ventricular cavity (RV) beneath the letters RV and just above the label denoting the septum (S). AML, aMVL = anterior leaflet of the mitral valve; ANT = anterior; Ao, AO = aorta; INF = inferior; LA = left atrium; LV = left ventricle; LVPW = left ventricular posterior wall; PML, pMVL = posterior leaflet of the mitral valve; POST = posterior; SUP = superior.

when the moving images are viewed in real time. A 4.5 or 7 megahertz 20 element transducer was employed in all patients.

Real time observations were made in sagittal and transverse planes with respect to the position and the phasic characteristics of the tricuspid valve, right ventricle and interventricular septum. Specific note was made of the location of the tricuspid valve leaflet relative to the normal position of the mitral valve. In all patients transverse imaging resulted in visualization of both the tricuspid and mitral valves.

Dimensions and excursions were measured from M mode recordings selected from the multiscan array and were compared with normal echocardiographic dimensions related to body surface area.[17]

Results

Normal subjects: The normal anatomic features as observed in a sagittal cross section (Fig. 2) have been described in detail previously.[22,23] The anterior right ventricle is at the left of the image with the interventricular septum posterior to the right ventricular cavity and in continuity with the anterior wall of the aorta. In patients with right ventricular enlargement, the interventricular septum appears to be more posterior. Tricuspid valve motion may be visualized within the cavity of the right ventricle in these patients. The longitudinal aspects of septal motion have been described previously by us[26] and others.[27] The septum exhibits a pivotal point below which normal posterior septal motion exists at the level of the chordae tendineae. The anterior and posterior mitral valve leaflets are seen within the left ventricle. The anterior leaflet of the mitral valve is continuous with the posterior wall of the aorta.

In the transverse view (Fig. 3), the tricuspid valve lies at the rightward and most anterior portion of the cardiac cross section. Only small portions of the inter-

TABLE I
Cross-Sectional Echocardiographic Findings in 10 Patients With Ebstein's Malformation

	Patients (no.)
Inferior displacement of tricuspid valve in sagittal view	9
Leftward displacement of tricuspid valve in transverse view	9
Increased right ventricular dimension	9
Systolic anterior septal motion	9; 1 equivocal
Abnormal tricuspid valve echoes	
Multiple	7
Elongated	7
Thickened	6
Increased tricuspid valve excursion	5
Whipping motion of tricuspid valve	3
Decreased right ventricular dimension	1

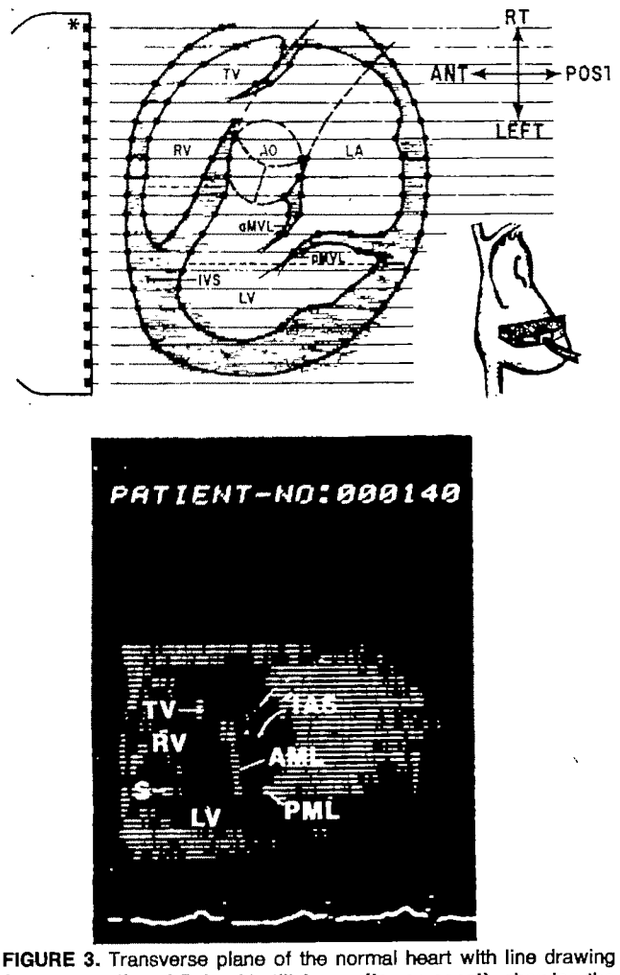


FIGURE 3. Transverse plane of the normal heart with line drawing **(upper panel)** and Polaroid still frame **(lower panel)**, showing the ventricular and A-V valve anatomy. The transducer position is shown in the insert, and image orientation is demonstrated by the compass. The normal anterior tricuspid valve leaflet (TV) occupies the anterior right portion of the image. The leaflet is short, discrete and significantly to the right of the anterior leaflet of the mitral valve (aMVL, AML). Fragmentary visualization is obtained of the interventricular septum (IVS, S) and the interatrial septum (IAS) because there is considerable echographic "dropout." The origin of the aorta (AO) is projected above the plane of the cross section **(dotted lines, upper panel)**. RT = right; other abbreviations as in Figure 2.

atrial septum are visualized because the septum lies in a plane almost parallel to the ultrasonic beam. An oblique section of the right ventricular cavity bordered by the interventricular septum lies to the left of and anterior to the tricuspid valve. The mitral anulus and anterior mitral leaflet are posterior to the interventricular septum and separated from it by the width of the left ventricular outflow tract.

Ebstein's malformation (Table I): In all but 1 of the 10 patients with Ebstein's malformation there was inferior displacement of the tricuspid valve within the right ventricle in the sagittal plane (Fig. 4) and leftward displacement of this valve in the transverse view (Fig. 5 and 6). The exception was a patient who had Ebstein's malformation associated with pulmonary valve stenosis and a hypoplastic right ventricle. In seven patients the tricuspid valve produced a distinctive pattern of multiple echoes. No single discrete tricuspid valve leaflet echo could be recorded, irrespective of gain control setting. Elongated tricuspid valve leaflets were noted in the seven patients, and in six the leaflets were thickened. Increased excursions of the tricuspid valve leaflets were noted in five patients. An overall effect observed in three patients when viewing images in real time was a "whipping" motion of the tricuspid valve.

The right ventricular dimension was increased in 9 of the 10 patients studied. Systolic anterior septal motion at or below the plane of the mitral valve was noted in nine patients.

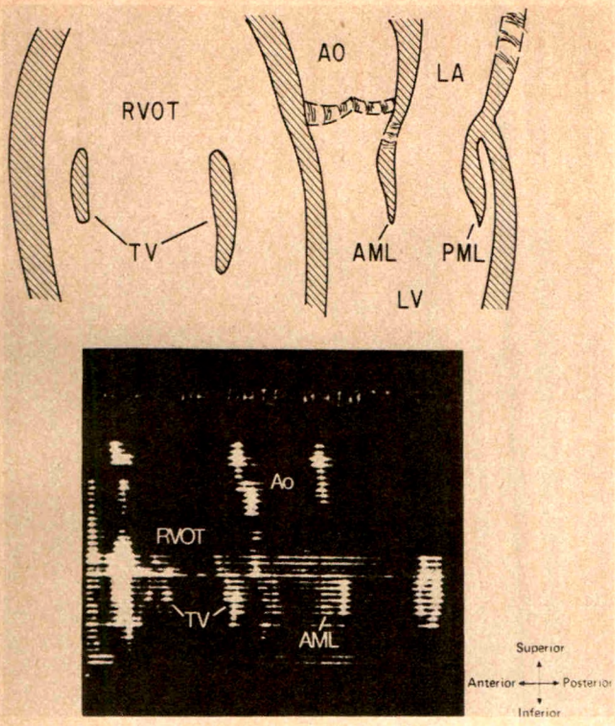
Right ventricular overload due to other congenital heart lesions: In a series of 100 consecutive examinations performed in children with various forms of congenital heart disease, only one false positive diagnosis of Ebstein's anomaly was made in a patient with hypoplasia of the left ventricle and marked enlargement of right-sided cardiac structures. An additional 15 patients with a moderate-sized atrial septal defect and significant right ventricular volume overload underwent multiscan examination. All demonstrated an increased right ventricular diameter with paradoxical motion of the intraventricular septum. In no instance was an elongated or displaced tricuspid valve seen.

Discussion

Specific echocardiographic features: Distinctive multiple crystal echocardiographic findings were observed in 10 patients with Ebstein's anomaly of the tricuspid valve. The principal diagnostic observation was inferior and leftward displacement of the tricuspid valve. Additional findings of importance included an easily recognized pattern of multiple echoes produced by the tricuspid valve and a "whipping" motion of the elongated tricuspid valve leaflets. Of lesser diagnostic significance were findings of elongated and thickened tricuspid valve leaflets, increased right ventricular dimension, increased excursion of the tricuspid valve leaflets and systolic anterior ventricular septal motion.

Correlation with anatomic findings: A spectrum of severity exists with respect to the two characteristic anatomic features of Ebstein's anomaly, namely, redundancy of valve tissue and adherence of a variable portion of the septal and posterior cusps to the right ventricular wall.[1] The redundancy may involve all cusps although the anterior cusp is usually less affected. The degree of adherence differs from patient to patient. Occasionally, little or no adherence exists and the false origin of the cusps is situated at the true atrioventricular (A-V) anulus. In some patients the adherence may extend to the ring formed by the parietal band, crista supraventriculus, septal band, moderator band and anterior papillary muscle.

The adherence and redundancy of the tricuspid valve leaflets displaces the apparent origin and the free edge of the tricuspid valve in a leftward and inferior direc-



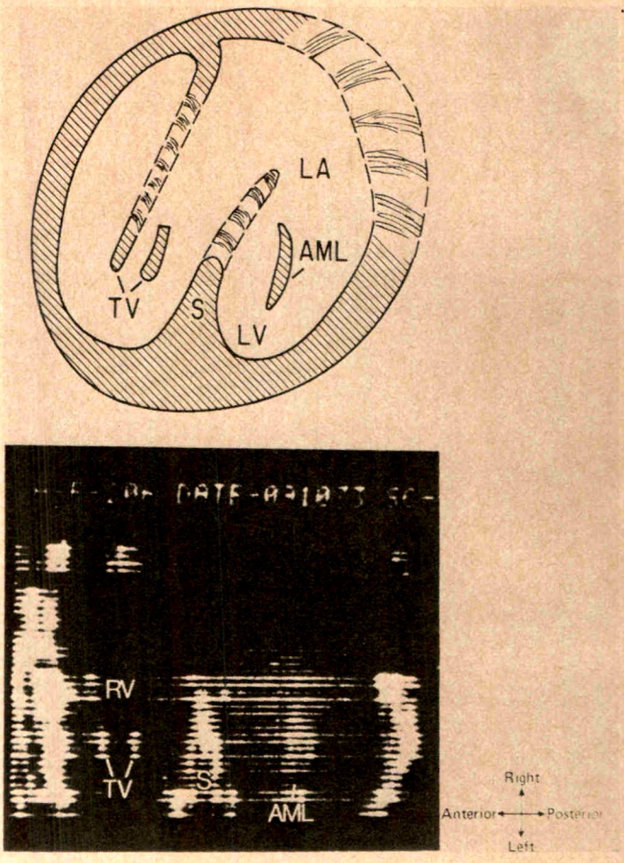


FIGURE 4 (above). Line drawing **(upper panel)** and an enlarged Super 8 mm still frame **(lower panel)** illustrate a sagittal cross section in a 15 year old patient with Ebstein's anomaly. The tricuspid valve (TV) is located in a more inferior position than normal. The right ventricle and right ventricular outflow tract (RVOT) are dilated. Abbreviations as in Figure 2.

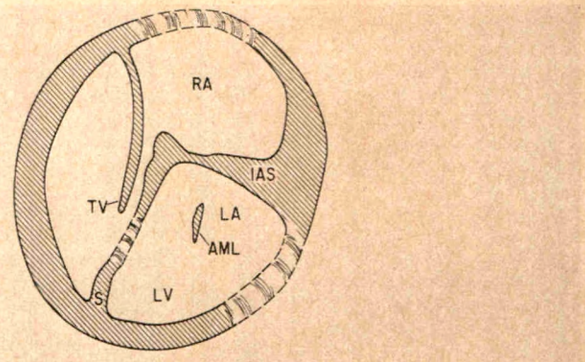


FIGURE 5 (top right). Same patient. Line drawing **(upper panel)** and an enlarged Super 8 mm still frame **(lower panel)** illustrating the transverse plane anatomy. The tricuspid valve (TV) extends leftward and anterior to the anterior mitral leaflet (AML). A dilated right ventricle (RV) is noted, thus placing a larger than usual portion of the ventricular septum (S) parallel to the transducer beam. Hence, echographic dropout occurs and the septum is only partially visualized. Abbreviations as in Figure 2.

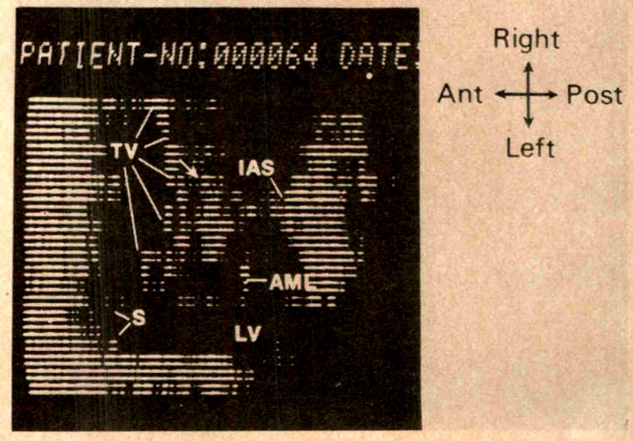


FIGURE 6 (bottom right). Line drawing **(upper)** and Polaroid still frame **(lower)** illustrating the transverse plane at the level of the anterior mitral leaflet (AML) in a 1 year old patient with Ebstein's malformation. The long redundant anterior leaflet of the tricuspid valve (TV) is displaced toward the left and in front of the anterior mitral leaflet. The junction **(white arrow)** of the interventricular (S) and interatrial (IAS) septa is imaged. Echographic dropout prevents visualization of the entire ventricular septum. RA = right atrium; other abbreviations as in Figure 2.

tion. In single crystal echocardiographic studies in patients with Ebstein's anomaly, echoes from the anterior tricuspid leaflet may be observed with the transducer placed quite laterally on the precordium.[5,9] The cross-sectional approach allows the visualization of lateral and inferior displacement and simultaneously demonstrates the positional relation between the tricuspid and mitral valves.

Advantage of cross-sectional technique: Confirmation was achieved with the current cross-sectional studies of abnormalities described previously with single crystal techniques. When viewed in sagittal cross section, the tricuspid leaflets appeared less discrete than normal and their redundancy produced multiple echoes. The redundant leaflets appeared elongated and thickened and moved with excessive excursion and an abnormal "whipping" motion. Motion of the interventricular septum is visualized well with the cross-sectional approach because the entire septum may be visualized in the sagittal plane. Systolic anterior motion has been emphasized as a specific finding in patients with right ventricular volume overload.[26,27] Our findings indicate that both the latter abnormal motion and right ventricular enlargement are nonspecific observations in patients with Ebstein's anomaly.

The atrialized portion of the right ventricle has been visualized by others[16] using a sector scanning cross-sectional technique. The phased array device used in our study did not provide visualization of the attachment of the tricuspid valve to the right A-V ring. Thus, we could not define the boundaries of the atrialized right ventricle. Whether high resolution systems will allow routine analysis of atrialized ventricle remains speculative. Our study indicates that real time cross-sectional echocardiography provides a rapid and simple means for accurate diagnosis of Ebstein's anomaly.

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Atrial Defect Size After Blalock-Hanlon Atrioseptectomy

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In transposition of the great arteries, a Blalock-Hanlon closed atrial septectomy is performed to improve intracardiac mixing at the atrial level. Although the Blalock-Hanlon septectomy is a common surgical procedure in cyanotic congenital heart disease, it has not been adequately assessed pathologically. In 14 heart specimens from patients (aged 3 days to 19 years) with transposition of the great arteries and Blalock-Hanlon septectomy, the margins of the septectomy, fossa ovalis and atrial septum were identified. The total area of the septum and its defects was calculated using planimetry. The ratio of defect size to atrial septal area was expressed as percent communication, which ranged from 5 to 39 (mean 18) percent in eight specimens with intact limbus of the foramen ovale and 26 to 57 (mean 42) percent in six specimens in which the limbus had been excised. The finding that specimens in which the Blalock-Hanlon defect extended into the fossa ovalis had the largest total communication emphasizes that to obtain optimal bidirectional atrial mixing the surgeon should extend the Blalock-Hanlon procedure across the limbus into the foramen ovale.

In transposition of the great arteries, the rationale for performing a Blalock-Hanlon closed atrial septectomy is to improve intracardiac mixing at the atrial level. In this procedure the surgeon isolates the interseptal area of the right and left atria with a curved clamp and excises the posterosuperior portion of the septum through incisions in the free wall of the right and left atria. Enlargement of this interseptal defect is possible if the clamp is loosened momentarily and the edges of the septum along the clamp are pulled closer toward the operator and excised.[1,2]

Although the Blalock-Hanlon atrial septectomy is a common surgical procedure in cyanotic congenital heart disease, the size and shape of the defect have not been adequately assessed anatomically or pathologically or related to clinical results. This paper describes the location and area of the Blalock-Hanlon atrial septectomy in anatomic specimens, emphasizing the value of extending the incision into the area of the fossa ovalis.

Materials and Methods

Heart specimens from the cardiac pathology collection at the Johns Hopkins Hospital with dextrotransposition of the great arteries and previously performed Blalock-Hanlon atrial septectomy were examined. All specimens had been fixed in formalin and transferred to Kaiserling's solution; the entire atrial septum, fossa ovalis and atrial septectomy could be identified in all specimens.

Specimens were from patients admitted to the Johns Hopkins Hospital from the late 1950's through 1975. Hypoxemia and metabolic acidosis predating more effective intensive care programs undoubtedly contributed to the high (60 percent) postoperative mortality rate in the group of patients reported on from this institution in 1966.[3]

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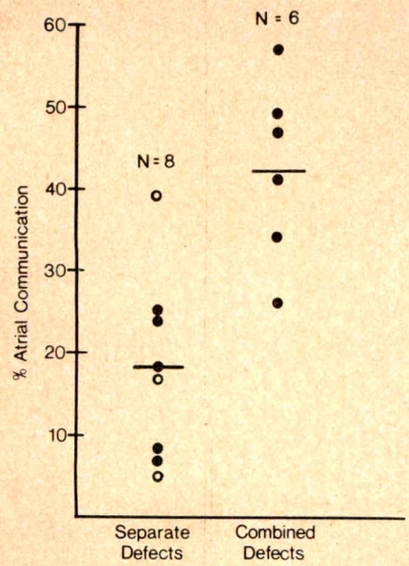


FIGURE 1. Ratio of atrial defect size to atrial septal area (expressed as percent communication) in hearts with a Blalock-Hanlon defect. Specimens in which the Blalock-Hanlon defect remains separated from the fossa ovalis defect have a smaller percent communication than those in which the Blalock-Hanlon defect extends into the fossa ovalis. **Open circles** represent specimens with a naturally occurring secundum atrial septal defect contributing to the total percent communication. N = number of specimens.

The margins of the septectomy, fossa ovalis and atrial septum were determined by manually securing the specimen in a fixed position with the atrial septum under uniform tension in its natural anatomic curvature. Special care was taken to not distort the margins of the Blalock-Hanlon atrial septectomy. The margins of the atrial septum were identified by probing the medial wall of the right atrium with a stainless steel pin placed at right angles to the septum and marking the portions of the medial wall that were common to the right and left atria but that contained no free wall of either chamber. The outlines of this margin were transferred to graph paper and areas of the atrial septum and defects were calculated using standard planimetry. The ratio of measured atrial defect size to atrial septal area was expressed as percent communication.

Included in the specimen review were three hearts from neonates less than 1 month of age, three from infants between 1 month and 1 year and eight from patients aged 1 year to 19 years. In nine cases, the Blalock-Hanlon atrial septectomy had been performed recently (within 2 weeks of death); in the other five, death occurred 5 weeks or more after the Blalock-Hanlon atrial septectomy. In the latter specimens the margins of the septectomy were always well healed and smooth.

Results

The percent communication for the Blalock-Hanlon atrial septectomy alone or in addition to an ostium secundum atrial septal defect ranged from 3 to 57 (Fig. 1). It ranged from 3 to 25 in specimens in which the septectomy did not extend into the fossa ovalis (Fig. 2) and from 5 to 39 in specimens in which the septectomy was augmented by a secundum defect. Two of the latter specimens had a small secundum defect (2 and 3 percent communication, respectively), but one specimen had a larger secundum defect (20 percent communication) (Table I, Fig. 1).

Specimens in which the Blalock-Hanlon atrial septectomy extended into the fossa ovalis (Fig. 3) typically had the largest percent communication (26 to 57) (Table II, Fig. 1). The specimens with the largest percent communication were not necessarily those in which the septectomy had been performed more than 5 weeks before death because one infant aged 4 days had the largest ratio of atrial defect size to atrial septal area.

Discussion

It is now established that patients with transposition of the great arteries and a naturally occurring atrial septal defect[4,5] or balloon septostomy[6,7] have an improved prognosis over patients without an atrial site for bidirectional mixing between the two circulations. Frequently, however, the defect produced by balloon

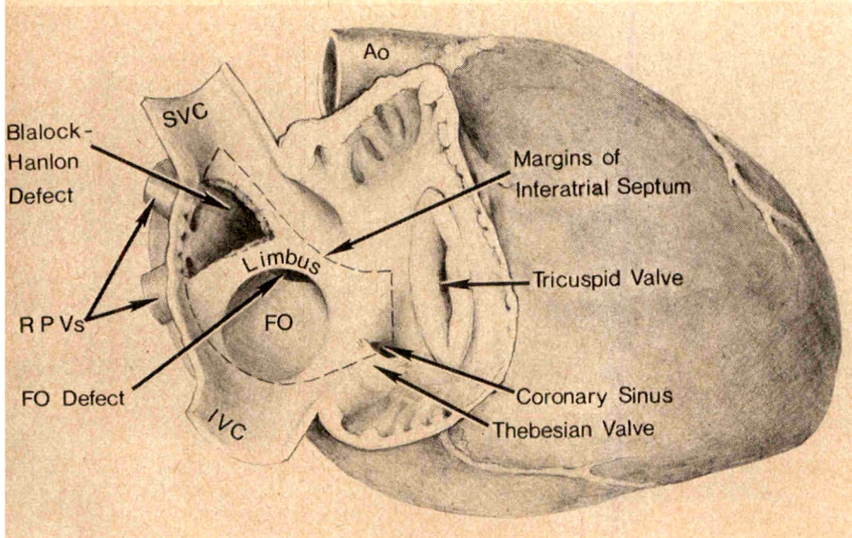


FIGURE 2. Opened right atrium in a heart with transposition of the great arteries. The fossa ovalis (FO) and Blalock-Hanlon defects are separated by the limbus of the fossa ovalis. Ao = aorta; IVC and SVC = inferior and superior venae cavae; RPVs = right pulmonary veins.

TABLE I

Separate Blalock-Hanlon and Fossa Ovalis Defects

Case no.	Area (mm^2)			Total Percent Communication	Age	
	Atrial Septum	Blalock-Hanlon Defect	Fossa Ovalis Defect		At Surgery	At Death
1	214	39	0	18	2 days	3 days
2	297	40	10	17	2.5 mo	4 mo
3	345	24	0	7	2.5 mo	2.5 mo
4	506	123	0	24	1.5 yr	1.5 yr
5	545	15	10	5	2 yr	2.5 yr
6	1066	197	216	39	10 yr	12 yr
7	1146	90	0	8	3.5 yr	3.5 yr
8	1340	303	0	25	2 yr	19 yr

TABLE II

Combined Blalock-Hanlon and Fossa Ovalis Defects

Case no.	Area (mm^2)		Percent Communication	Age	
	Atrial Septum	Combined Defect		At Surgery	At Death
9	145	37	26	2 days	3 days
10	166	94	57	2 days	3 days
11	195	66	34	5.5 yr	5.5 yr
12	526	248	47	1 yr	1 yr
13	664	324	49	5 mo	5 mo
14	948	240	41	8 yr	8 yr

septostomy becomes inadequate before the child has reached sufficient size and weight for a Mustard procedure. In these cases a Blalock-Hanlon atrial septectomy often improves bidirectional shunting at the atrial level.[8,9] While ventricular compliance and pulmonary blood flow are important to the success of the atrial septectomy in improvement of atrial mixing, a large atrial communication seems to be the most desirable prerequisite.[10,11]

Our specimen review indicates that the largest percent communication is present when the limbus of the foramen ovale is included in the excised tissue. This may be the result of loss of structural integrity of the foramen portion of the septum so that the communication enlarges further as the atria with their septum enlarge with somatic growth. Of interest is that the largest percent communication found in a specimen without limbus excision had a naturally occurring ostium secundum atrial septal defect, an infrequent finding in transposition of the great arteries.[4]

This study emphasizes that when closed atrial septectomy is undertaken, particular attention should be directed to excision of the limbus of the fossa ovalis. With inclusion of the limbus in the surgical specimen, one can expect a larger atrial communication, which will optimize bidirectional interatrial mixing.

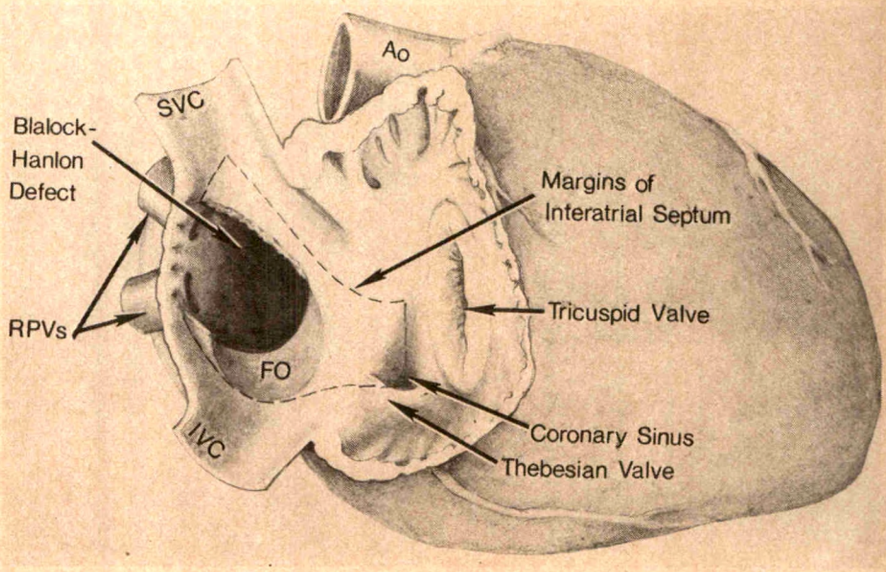


FIGURE 3. Opened right atrium in a heart with transposition of the great arteries to demonstrate the combined Blalock-Hanlon and fossa ovalis defect that results from excision of the limbus of the fossa ovalis. Abbreviations as in Figure 2.

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Intravenous Diazoxide Therapy in Hypertensive Crisis

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Ninety-one doses of diazoxide were administered intravenously to 41 patients with hypertensive crises. Diastolic blood pressure was reduced from an average of 139 to 98 mm Hg within 10 minutes. On the basis of a retrospective analysis of the response of diastolic blood pressure, it was possible to determine within 10 minutes of injection whether a second dose would be required. Therapy was judged to be effective in 38 of 41 patients; 35 percent of injections were ineffective. Concomitant administration of furosemide was not shown to have a beneficial antihypertensive effect. Mean blood urea nitrogen was 59.5 mg/100 ml initially and was not significantly different 2 weeks after therapy. None of the patients demonstrated clinical evidence of diazoxide-induced deterioration of coronary circulation. Electrocardiograms obtained 2 weeks after diazoxide therapy failed to show evidence of new ischemic changes. Only 9 percent of patients complained of side effects, and these were transient and relatively innocuous. It is concluded that diazoxide is both safe and efficacious in the management of hypertensive crises.

The introduction of the benzothiadiazine derivative diazoxide has been a significant advance in the therapeutic approach to the hypertensive crisis. Several reports[1–8] attest to the efficacy and safety of this compound. The rapidity with which control of blood pressure is achieved has led to a reevaluation of the therapeutic goals in managing the severely hypertensive patient.

To evaluate further the effectiveness and safety of diazoxide in the clinical setting, a multicenter study was undertaken. Patients presenting with severe hypertension were treated with intravenously administered diazoxide and carefully evaluated over the ensuing 2 weeks. The results demonstrated that diazoxide safely, rapidly and effectively reduces blood pressure and is useful in treating most hypertensive crises.

Methods and Materials

Protocol: Five centers participated in the study. Forty-one patients, judged to have hypertension of sufficient severity to warrant rapid reduction of blood pressure, were entered into the protocol. Age, sex, race, weight, concurrent disease, medications, basal blood pressure and pulse were recorded. Blood was drawn for determinations of glucose, urea nitrogen, uric acid and creatinine levels. Electrocardiograms and chest X-ray films were obtained. A total of 91 doses of diazoxide were administered intravenously to the study group of 41 patients. Eighty-nine doses were injected over a period not exceeding 30 seconds, and 2 doses over a 1 minute period. In 11 instances, the dose was less than, and in 4 instances greater than, 300 mg; in the remaining 76 injections, the dose was 300 mg. Blood pressure, pulse and symptoms were recorded 2, 5, 10, 15, 45 and 75 minutes and 2, 4, 8, 12, 24, 36 and 48 hours after injection. Concurrently administered antihypertensive medications were recorded. The variables cited were monitored over the succeeding 2 weeks. Mean blood pressure was calculated from the formula: mean blood pressure = diastolic blood pressure plus one third of pulse pressure.

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TABLE I

Number of Courses and Injections per Course

Injections (no.)	Courses (no.)*
1	22
2	13
3	6
4	2
5	1
6	2
Total	46

* A course of treatment is defined as a series of injections, no two of which are more than 120 hours apart.

A single course of diazoxide therapy was arbitrarily defined as a single injection or a series of injections, no two of which were more than 120 hours apart. Several patients received more than one course of diazoxide therapy.

Assessment of effectiveness: Each investigator subjectively assessed the effectiveness of diazoxide therapy in the patients for whom he was responsible. In addition, objective data were obtained to corroborate and support the clinical assessment. An injection was classified effective if diastolic blood pressure decreased by more than 30 mm Hg or to less than 100 mm Hg within the first 10 minutes of administration and if the reduction was sustained for at least 75 minutes. Transient effectiveness was defined as a similar reduction of blood pressure not sustained for 75 minutes. An ineffective injection was one that failed to result in this decrement of blood pressure.

Demographic data: Forty-one patients aged 23 to 71 years were studied. There were 26 men and 15 women whose weights ranged from 47.3 to 128.2 kg. The number of injections per course and the courses of injections are shown in Table I. Three patients received more than one course of therapy. Seventy-five percent of the courses consisted of one or two injections. Nine patients were without concurrent disease. Four patients had a history of coronary artery disease and four a history of occlusive cerebrovascular disease. Seventeen had significant renal dysfunction, but none was undergoing long-term dialysis at the initiation of this study. The remaining diagnoses were varied and unrelated to the cardiovascular system. Three patients died within 2 months of diazoxide therapy. These deaths, occurring 8, 23 and 54 days, respectively, after treatment, appeared to be unrelated to diazoxide therapy.

Results

Blood pressure: For purposes of analysis, the patients were classified into three groups: those who received one injection (18 patients) and those who received two (13 patients) or more (10 patients) injections.

The blood pressure response of patients receiving a single injection of diazoxide is shown in Figure 1. Four of the patients in this group had two courses of therapy. The average (± standard error of the mean) pretreatment systolic, diastolic and mean blood pressures were 229 ± 4.4, 139 ± 3.5 and 169 ± 3.9 mm Hg, respectively. Within 10 minutes, average systolic and diastolic pressures were reduced to 166 ± 6.9 and 98 ± 4.0 mm Hg, respectively. Generally, blood pressure remained at these levels for the first 48 hours after therapy.

The response of mean blood pressure in 13 patients receiving two injections is shown in Figure 2. The initial mean blood pressure of 178 ± 4.6 mm Hg is not different from that observed in patients requiring only a single injection. The reduction in blood pressure resulting from the first injection in this group of patients was maximal at 2 minutes, decreasing to 139 ± 7.5 mm Hg. The subsequent rise toward pretreatment values necessitated the second injection. The mean pressure decreased to 128 ± 8.8 mm Hg within 2 minutes after injection

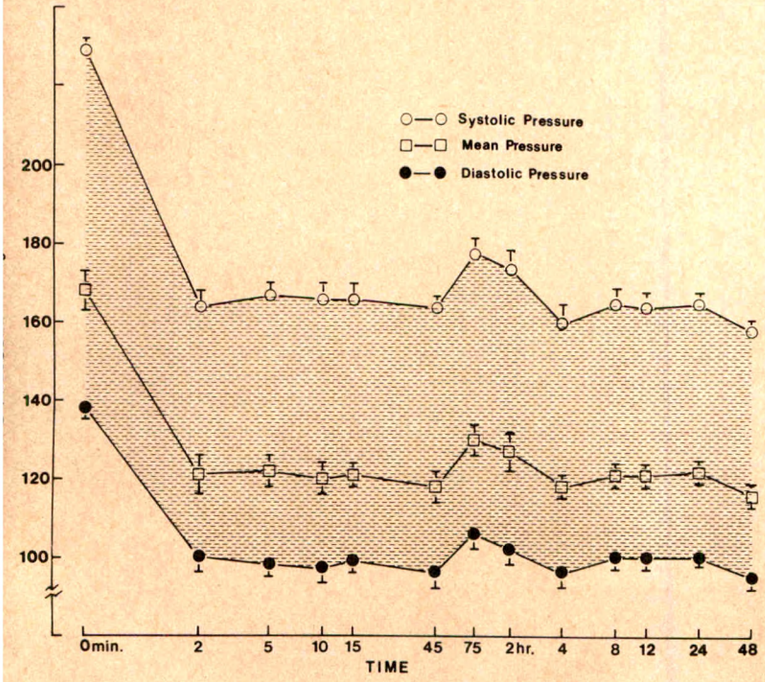


FIGURE 1. Systolic, diastolic and mean blood pressure (± standard error of the mean) in 18 patients receiving a single injection of diazoxide.

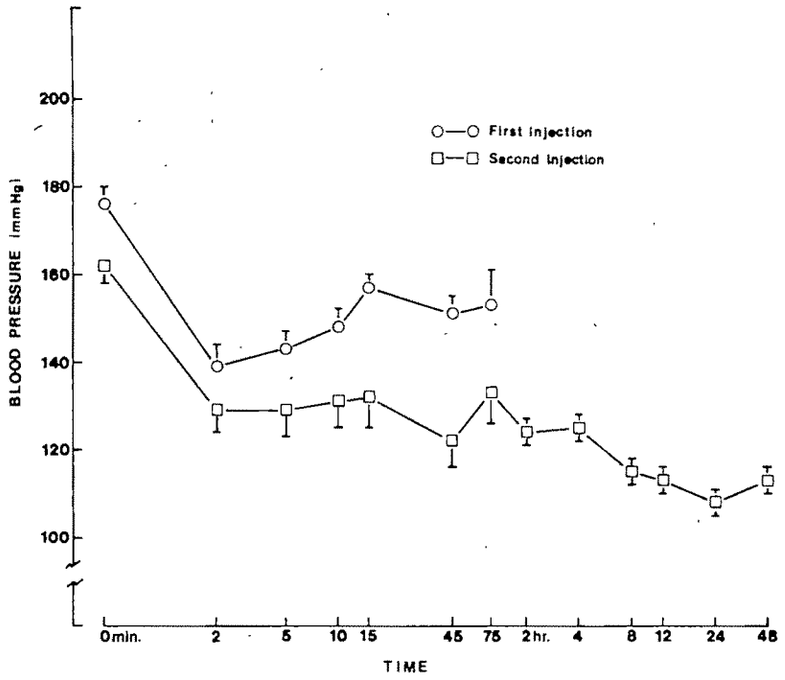


FIGURE 2. Mean blood pressure (± standard error of the mean) in 13 patients receiving two injections of diazoxide. Response to the first injection is plotted for only 75 minutes because of insufficient observations beyond that time.

of the second dose. Subsequently, the blood pressure tended to decrease during the next 48 hours.

The mean blood pressure response observed in 10 patients receiving more than two injections is illustrated in Figure 3. The changes in pressure induced by the first and last doses are shown. Response to the first dose was inadequate and this was apparent in most cases within 75 minutes. The last injection generally resulted in a rapid initial reduction of mean pressure and a subsequent progressive decrease over the next 48 hours.

Effectiveness of diazoxide therapy: Each investigator was asked to assess subjectively the effectiveness of diazoxide therapy in the patients for whom he was responsible. By these criteria, diazoxide was judged effective in 38 of 41 patients.

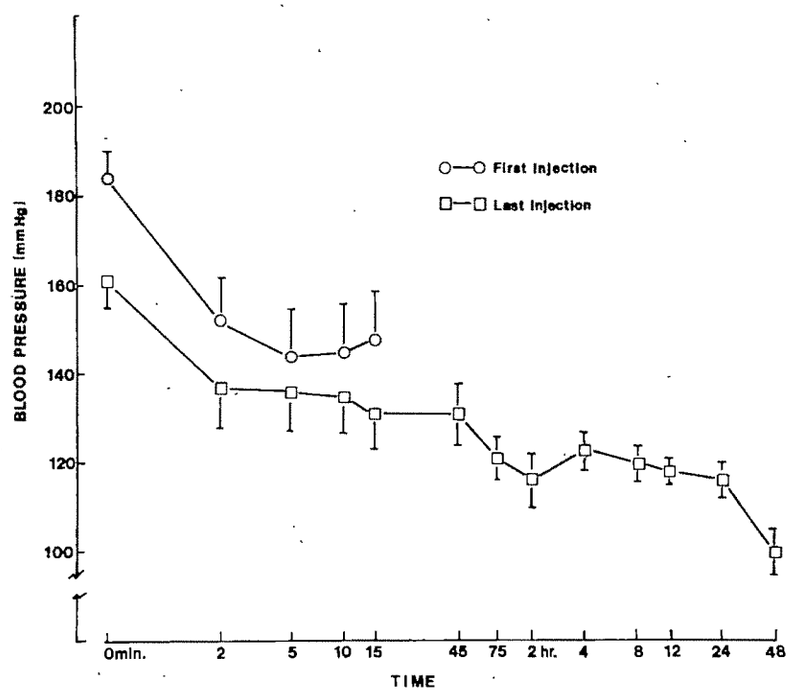


FIGURE 3. Mean blood pressure (± standard error of the mean) in 10 patients receiving more than two injections of diazoxide. Data from first and last injections are plotted. Response to the first injection is plotted for 15 minutes only because of insufficient observations beyond that time.

TABLE II

Time When Maximal Reduction in Diastolic Pressure Was Obtained After the First, Second or Subsequent Injection of Diazoxide

Time After Injections (min)	Injections					
	First		Second		Subsequent	
	no.	%	no.	%	no.	%
2	9	23	8	35	6	32
5	11	28	5	22	4	21
10	7	18	0	0	3	15
15	3	7	5	22	1	5
45	5	13	1	4	1	5
75	3	7	4	17	2	11
120	2	5	0	0	2	11
Total	40	100	23	100	19	100

Figures in parentheses refer to percent of injections eliciting maximal response at that time. Of the 91 injections 9 could not be analyzed because of insufficient data.

With use of the more objective criteria, 84 of the 91 injections could be classified; missing data points made it impossible to classify the remaining 7 injections. By these criteria, 47 injections (55 percent) were effective and 8 (10 percent) were transiently effective. Twenty-nine injections (35 percent) were classified ineffective. Expressed as milligrams per kilogram, the doses for these three groups were 4.9, 4.7 and 4.0, respectively, not significantly different from each other.

Time of maximal blood pressure reduction: Each response to diazoxide was analyzed to determine when, within 4 hours of injection, maximal diastolic pressure reduction was obtained (Table II). Fifty percent of first injections resulted in a maximal reduction of diastolic pressure within 15 minutes. Similar patterns were observed after 23 second injections and the 19 third or subsequent injections.

The data were further analyzed to determine how frequently the diastolic pressure reduction obtained within the first 10 minutes of injection was within 10 mm Hg of the lowest diastolic reading obtained within the first 2 hours. After the first injection of diazoxide, 40 of 41 patients (97 percent) fulfilled these criteria. For the second or subsequent injections, the corresponding figure was 36 of 45 patients (80 percent). If the observation period for second or subsequent injections was extended from 10 to 15 minutes, the diastolic pressure in 39 of 45 patients (87 percent) was within 10 mm Hg of the lowest obtained reading. In no instance did diastolic pressure, after 10 minutes, decrease by more than 30 mm Hg during the subsequent 2 hours.

In only six patients was diazoxide given within 30 minutes of a previous injection. In none of these patients was the response to the second dose greater than the response to the first.

Influence of renal function on blood pressure response: The response to the first injection of diazoxide was evaluated as a function of pretreatment levels of blood urea nitrogen and creatinine. Data were sufficient in 36 of the 41 patients to permit analysis. Eighteen patients had an effective response to the first injection; mean blood urea nitrogen and creatinine were 61 and 5.4 mg/100 ml, respectively, for these patients. For the 16 patients who failed to respond, mean blood urea nitrogen and creatinine were not significantly different (65 and 6.3 mg/100 ml, respectively). Two of the injections were transiently effective and mean blood levels for these patients were 24 and 1.9 mg/100 ml, respectively. The response to diazoxide in these patients did not correlate with pretreatment renal function.

Concomitant use of furosemide: Although no attempt was made to control the use of other orally administered antihypertensive agents, the response to diazoxide was analyzed with respect to the concomitant use of furosemide. Seventy-seven injections could be analyzed; furosemide was administered in conjunction with 48 of these. Forty-three percent of the

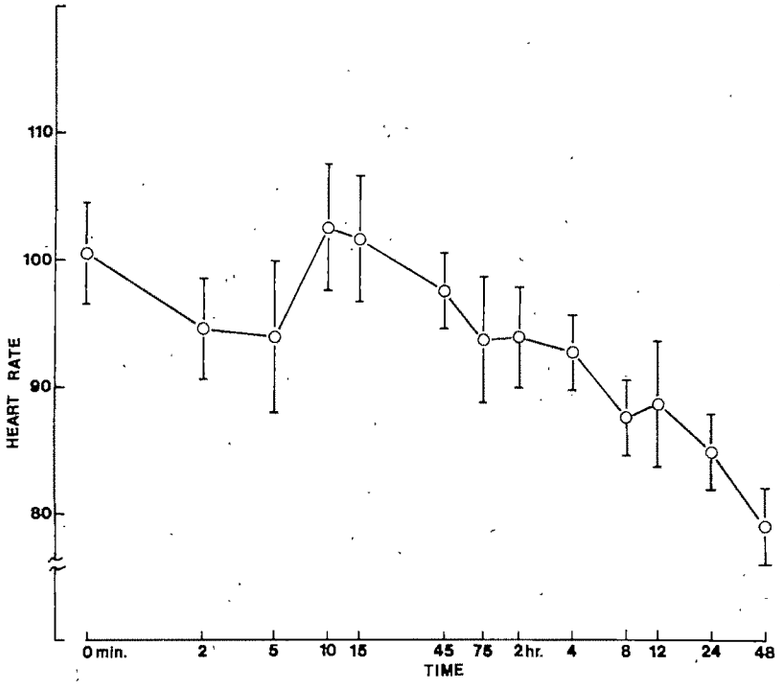


FIGURE 4. Change in heart rate in patients receiving a single dose of diazoxide.

TABLE III

Pulse Rate Before Diazoxide and Maximal Percent Increase and Decrease After Administration of Diazoxide in Patients Receiving Single or Multiple Injections (mean ± standard error of the mean)

	Initial Pulse Rate (beats/min)	Maximal % Increase	Maximal % Decrease
Single injection	100.7 ± 4.9	3 ± 3.6	20.3 ± 4.0*
(no.)	17	17	17
Multiple injections	102.2 ± 3.2	12.8 ± 2.1*	10.5 ± 2.3*
(no.)	65	56	56

* Difference from initial pulse rate ($P < 0.01$).
Data are based on the first 48 hours after injections.

injections were successful when furosemide was simultaneously administered and 57 percent were effective when the diuretic drug was not utilized. In this series, furosemide could not be shown to favorably affect the response of diazoxide.

Response of heart rate to diazoxide (Fig. 4 and Table III): Pulse rate initially decreased slightly after administration of diazoxide but returned to pretreatment levels by 10 minutes. A gradual decrease ensued and the rate decreased below pretreatment values by 8 hours. The maximal percent increase in pulse rate shown in Table III was significant only for the group receiving multiple doses. The maximal decrease in heart rate was significant in patients receiving either single or multiple injections of diazoxide. Concomitant use of sympathetic blocking agents did not appear to influence significantly the subsequent response of heart rate to diazoxide.

Funduscopic findings: Changes in retinopathy 2 weeks after therapy are shown in Table IV. Ninety percent of the patients had either grade 3 or grade 4 retinopathy (Keith-Wagener-Barker classification) before therapy; 2 weeks after therapy only 51 percent had retinopathy of equal severity.

Effect of diazoxide on glucose metabolism: The mean blood glucose before administration of diazoxide was 133.4 mg/100 ml. The highest mean glucose value obtained during the first 48 hours after therapy was 139.8 mg/100 ml. The highest glucose value obtained during therapy in any individual patient was 308 mg/100 ml, which represented an increase from the value of 223 mg/100 ml before therapy. In this series of patients, diazoxide did not have a major detrimental effect on glucose metabolism.

Alterations in renal function induced by therapy: Mean blood urea nitrogen and creatinine values were 58 and 5.5 mg/100 ml, respectively, before administration of diazoxide. Two weeks after diazoxide therapy, these values were unchanged (59 and 5.7 mg/100 ml, respectively). Only eight patients demonstrated an increase in blood urea nitrogen of more than 50 percent above the pretreatment level and a tendency for the level to rise after therapy. Only one patient had a more than 30 percent increase in creatinine.

Electrocardiographic effect of diazoxide: Thirty-nine of 41 patients had electrocardiographic evaluation before diazoxide therapy. Only one had a normal electrocardiogram. Of the remaining 38 patients, 4 had ST-T wave changes compatible with ischemia and an additional 2 had evidence of previous myocardial infarction. No patient had symptoms suggesting acute coronary artery disease.

During therapy, one patient had angina that occurred 20 minutes after administration of diazoxide, at a time when blood pressure was 250/158 mm Hg. This episode was not believed to be diazoxide-induced. Electrocardiograms were obtained in 35 patients 2 weeks after diazoxide therapy; no tracing demonstrated deterioration attributable to ischemia.

Other adverse effects (Table V): Only 8 of 91 injections (9 percent) were associated with side effects. The most serious of these was transient weakness of the right arm and hand that rapidly resolved.

Discussion

Mean reduction in blood pressure: For all injections of diazoxide, diastolic pressure decreased an average of 28 mm Hg (20 percent) within 2 minutes. For patients receiving only one injection of diazoxide, diastolic pressure decreased an average of 41 mm Hg (29 percent). These changes in diastolic pressure compare with previously reported decreases of 16[4] and 50 mm Hg[5] and 37 percent.[2] For all injections, the reduction of mean pressure within 2 minutes of diazoxide therapy was 33 mm Hg (20 percent). Comparable figures for patients receiving only one injection were 38 mm Hg (28 percent). These figures are similar to those previously reported, which ranged from 19 to 40 percent.[1,6–10]

Effectiveness: Subjectively, diazoxide was judged effective in 38 of 41 patients. Objectively, 55 percent of injections were effective, 10 percent transiently effective and 35 percent ineffective. By comparison, Miller et al.,[2] using similar criteria, reported that 78.5 percent of injections were effective, 7.7 percent transiently effective and only 13.8 percent ineffective.

Diazoxide is frequently used with potent diuretic agents to counteract its sodium-retaining properties and augment its antihypertensive effect. In this study we could not demonstrate that effectiveness was improved

TABLE IV

Changes in Retinopathy* 2 Weeks After Diazoxide Therapy

Before Therapy	After Therapy: Normal	I	II	III	IV	Patient Not Available	Totals
I	...	...	...	...	...	2	2
II	...	...	2	...	...	...	2
III	1	1	7	11	...	1	21
IV	...	...	6	2	5	3	16
Totals	1	1	15	13	5	6	41

* Classification according to criteria of Keith, Wagener and Barker.

TABLE V

Patient Complaints and Side Effects Related to Therapy

Injections (no.)	Complaints
3	Nausea and vomiting
1	Nausea
1	Warmth after injections
1	Orthostasis
1	Venous irritation
1	Weakness in hand and arm

by the addition of furosemide to the therapeutic regimen. The reason for this striking finding is not clear. Although no data are available, it is possible that this might be explained either by patient selection or by careful attention to fluid balance. In either case, the data demonstrate that the use of potent diuretic drugs in conjunction with diazoxide is frequently unnecessary.

Diastolic blood pressure has been reported to decrease maximally between 2 and 10 minutes after injection of diazoxide.[2] Although this was generally true in our study group, the greatest decrease in blood pressure was delayed at least 15 minutes after 35 percent of the injections. Nevertheless, after 97 percent of first injections and 80 percent of second or subsequent injections, the diastolic pressure observed within the first 10 minutes of injection was within 10 mm Hg of the lowest blood pressure level obtained during the subsequent 2 hours. Of those patients whose subsequent blood pressure measurements were significantly lower than those observed within 10 minutes, the further decrement never exceeded 30 mm Hg.

Pulse rate: Several investigators[11–15] have demonstrated that intravenous administration of diazoxide causes a significant increase in heart rate within 5 minutes of injection. It is not known whether this chronotropic effect is mediated by direct stimulation of the beta receptor sites in the heart or indirectly by stimulating carotid baroreceptor activity. In our study, administration of diazoxide resulted in a decrease in heart rate. The difference between these results and those previously reported may reflect the initial condition of patients. For example, the mean pulse rate before treatment in our cooperative study patients was 101 beats/min, in contrast to 74 beats/min reported in the patients of Bhatia and Frohlich.[11] It is possible that our study patients were initially under a greater degree of sympathetic stimulation and therefore less likely to respond to further sympathetic stimulation.

Retinopathy: The finding that approximately 40 percent of patients with retinopathy showed improvement during the posttreatment period of 2 weeks is not surprising and attests to the effectiveness of antihypertensive therapy. Small hemorrhages, soft exudates and papilledema have been demonstrated to clear within several weeks of control of blood pressure.[3,16] Larger retinal lesions may take many months to clear.

Renal function: Previous investigators[3,17–19] have reported at least transient increases in blood urea nitrogen associated with reduction of blood pressure. Although progressive renal deterioration has been observed with aggressive antihypertensive therapy,[17,18] several recent reports have emphasized the reversible nature of the induced azotemia.[3,19] Mrozcek et al.,[5] for example, reported increases of 19 and 17 percent, respectively, in mean blood urea nitrogen and creatinine 2 weeks after the initiation of intensive antihypertensive therapy. The increase was greater in those patients with initial blood urea nitrogen values greater than 60 mg/100 ml. Seven months after therapy, however, mean blood urea nitrogen and creatinine values were 35 and 4.5 percent, respectively, lower than pretreatment measurements.

In contrast to these findings, our patients demonstrated no increase in either mean blood urea nitrogen or creatinine 2 weeks after the initiation of therapy. Although this difference in findings does not appear to be related to the degree and rapidity of blood pressure reduction, an explanation is not readily apparent.

Electrocardiographic effects: A recent report[20] noted that 7 of 14 patients receiving diazoxide exhibited significant ST-T changes within 15 minutes of drug administration. Five of these patients also manifested chest discomfort and one had evidence of an acute myocardial infarction. Our results do not corroborate these findings and, in this respect, agree with the data of Miller et al.[2] None of our patients manifested either electrocardiographic or clinical cardiac deterioration. Although we believe that diazoxide is contraindicated in patients with an acute coronary artery syndrome, in most other settings it does not appear to have a significantly adverse effect on myocardial oxygenation.

Side effects: The incidence of drug-related side effects (9 percent) is comparable with the previously reported incidence rate of 12 percent.[2] Of note is the minor nature of these side effects. Only one reported symptom was related to cerebrovascular or coronary insufficiency. The infrequency of these side effects, despite the presence of severe coronary and cerebral atherosclerotic disease in at least 25 percent of the patients, may reflect the hemodynamic effects of this drug. Coincident with the induced reduction of blood pressure, cardiac output has been reported to increase by as much as 55 to 75 percent and peripheral resistance to decrease dramatically.[7,9] Additional protection from symptoms of coronary insufficiency may be provided by increased coronary blood flow[13,21] and the dramatic reduction in afterload on the heart. There were no episodes of severe hyperglycemia, blood sugar never attaining values greater than 308 mg/100 ml.

Clinical implications: Diazoxide continues to enjoy a reputation for both safety and efficacy. In an average hypertensive adult, 300 mg of diazoxide intravenously will result in a significant reduction in blood pressure in more than 50 percent of patients. The effectiveness of diazoxide can be gauged within 10 to 15 minutes of injection. Sodium retention may be countered with the use of potent diuretic agents. Blood glucose should be carefully monitored, but hyperglycemia occurs infrequently; other side effects are also uncommon. Renal function in most patients remains relatively stable in the immediate posttreatment period. Other manifestations of severe hypertensive diseases, such as retinopathy and tachycardia, are at least partially and rapidly reversed. Diazoxide appears to be an excellent drug for the initial treatment of the majority of clinically encountered hypertensive crises.

Acknowledgments

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Results and Complications of Intraaortic Balloon Pumping in Surgical and Medical Patients

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The intraaortic balloon was attempted for therapy in 94 patients and successfully placed in 86. The balloon catheter could not be passed through the femoral or iliac artery in 12 patients (13 percent) of the group; in 4 of these the balloon was inserted through an aortic arch graft. The medical indications were cardiogenic shock and preinfarction angina. Ten of the 14 patients in the group with shock survived when treated with an aortic balloon without emergency surgery. Indications for balloon pumping in the surgical group included inability to wean the patient from the pump-oxygenator, postoperative shock and prophylactic placement of the balloon for poor ventricular function. Inability to remove a patient from pump-oxygenator support was the most common surgical indication, and 47 percent of patients were long-term survivors. Only 1 of the 17 patients for whom balloon pumping was used prophylactically died. Complications occurred in 17 percent of the entire group of 86 patients although the rate for medical patients with cardiogenic shock was 50 percent. The most common complication was arterial insufficiency requiring removal of the balloon. Four patients had permanent damage to the legs from ischemia, one patient requiring bilateral amputation. The overall incidence of serious arterial obstruction was 10 percent. Other complications included balloon displacement with arterial obstruction and pericardial tamponade from anticoagulant agents resulting in death.

Intraaortic balloon pumping provides significant assistance to the heart and circulation during shock and low cardiac output.[1–3] It may also be used prophylactically and therapeutically for serious left ventricular dysfunction and impending infarction.[4] The potential advantages of this assistance are occasionally negated by a variety of complications or lack of accessibility to the thoracic aorta. The advantages and problems related to the variety of indications are the subject of this report.

Methods

Technique: The Avco intraaortic balloon system was used routinely in all patients. In the standard surgical approach the attending cardiac surgeon exposes the common femoral artery under local anesthesia, performs a longitudinal arteriotomy, inserts the balloon catheter under control of a tourniquet and anastomoses a 10 mm woven Teflon® arterial graft end to side with 4-0 Prolene suture. No balloon was inserted by a surgical resident except under the direct supervision of the attending surgeon. The tip of the balloon catheter was positioned just below the aortic arch with use of palpation and X-ray monitoring. For medical and preoperative applications a technique of continuous heparin and dextran infusions has been developed for anticoagulation with monitoring of activated clotting times to maintain approximately a 60 percent increase over baseline values. In postoperative applications no anticoagulation was used for 72 hours, then an anticoagulant regimen similar to the medical regimen was used. In the event of iliac arterial stenosis the other femoral artery was utilized. A size 20 cc

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TABLE I

Medical and Surgical Indications for Intraaortic Balloon Pumping and Survival

	Cases (no.)	Survivors no.	Survivors %
Surgical Indications			
Weaning from pump	34	16	47
Postoperative shock	11	3	27
Prophylactic	17	16	94
Unsuccessful passage	3	2	66
Total	65	37	
Medical Indications			
Cardiogenic shock (not operated on)	14	10	71
Hypotension* (not operated on)	1	1	...
Unsuccessful passage of balloon	5	1	20
Cardiogenic shock (operated on)	4	2	50
Crescendo angina	5	4	80
Total	29	18	

* The patient classified as having hypotension was originally considered to have cardiogenic shock.

TABLE II

Complications of Intraaortic Balloon Pumping in the Medical and Surgical Groups*

Complications	Patients (no.)
Surgical Group (no. = 65)	
Femoral arterial obstruction requiring balloon removal	3
Aortic insufficiency with temporary failure	1
Iliac arterial obstruction by displaced balloon	1
Tamponade secondary to anticoagulation	1
Hematoma of right thigh	1
Balloon removal because of poor cardiac function	1
Total	8 (12.9%)
Medical Group (no. = 29)	
Femoral arterial obstruction requiring balloon removal	2
Ischemic necrosis of calf	1
Gangrene of both legs	2
Gangrene of one leg	1
Dissection of aorta with temporary ischemia	1
Total	7 (29%)

* The percentages do not include the eight patients in whom the balloon could not be inserted.

balloon was tried if the 30 or 40 cc sizes could not be passed. Obstructive problems usually occurred in the upper iliac artery, and attempts to cannulate the iliac artery directly were not helpful. If the chest was open when iliac or femoral arterial stenosis was encountered, the balloon was placed by suturing a long woven Teflon graft to the aortic arch. The balloon catheter and graft were then brought out below the sternum through the epigastric portion of the sternal splitting incision.

Indications: The indications for use of intraaortic balloon pumping have increased with time in both medically and surgically treated patients. In our institution the principal medical indication has been cardiogenic shock resulting from myocardial infarction. The standard criteria used for the definition of unresponsive shock are systolic blood pressure less than 90 mm Hg, oliguria, vasoconstriction, elevated pulmonary arterial pressure and lack of response to administration of fluids and vasopressor agents. The other medical indication is preinfarction or crescendo angina, defined as prolonged recurrent anginal pain of increasing frequency, unresponsive to nitroglycerin or its analogs and associated with typical S-T segment changes and absence of serum enzyme elevations. Surgery was attempted only in four patients who were unresponsive to therapy with intraaortic balloon pumping and who could not be successfully weaned from the balloon.

In the surgical cases three indications are used: (1) inability to remove the patient from pump-oxygenator support because of shock or low cardiac output, (2) postoperative shock, and (3) prophylactic use in high risk patients with extremely poor ventricular function (ejection fraction less than 0.40). The definition of shock for the surgical group was the same as for the medical group.

Informed consent was obtained from each patient or a responsible family member.

Results

There were 29 medical and 65 surgical applications of the balloon pump in 4 years. Table I presents the indications, incidence of successful balloon passage and survival rates in the two subgroups. Table II presents the complications resulting from intraaortic balloon pumping in the medical and surgical groups.

Medical Group (29 Cases)

Ten of the 14 patients treated for cardiogenic shock after myocardial infarction without additional surgery were long-term survivors. Each patient with shock demonstrated a systolic blood pressure of less than 80 mm Hg, and most of the group had associated findings of oliguria, peripheral vasoconstriction and diaphoresis. In five patients the blood pressure was raised above 90 mm Hg by intravenous administration of pressor agents before insertion of the balloon. The one patient classified as having hypotension was originally considered to have cardiogenic shock but subsequently was reclassified because of a favorable response to fluid administration, presence of a low pulmonary arterial pressure and absence of criteria for acute myocardial infarction.

The balloon could not be placed successfully in five additional patients with cardiogenic shock because of iliac arterial obstruction. Only one of these patients survived. The five patients who were not given balloon therapy (25 percent of the group) because of unsuccessful passage of the balloon were all older than 70 years. The left subclavian arterial approach was also attempted in two patients but failed because of arterial stenosis in one patient and an inability to direct the balloon into the descending thoracic aorta in the other.

The four patients with cardiogenic shock treated with surgery in addition to balloon pumping had a large aneurysm in the area of acute infarction. These patients all had resection of the aneurysms; three had aortocoronary vein bypass grafts and one had mitral valve

TABLE III

Overall Complication Rate of Intraaortic Balloon Pumping*

Complications	Patients no.	Patients %
Overall incidence	15	17.4
Serious obstruction to circulation of leg	10	11.6
Unsuccessful passage of balloon through femoral artery	12	13
Aortic arch placement	4	5

TABLE IV

Reported Results of Intraaortic Balloon Pumping for Cardiogenic Shock Without Additional Surgery

	Patients Total no.	Patients Survivors (%)
Dunkman et al.[1]	25	18
Scheidt et al.[2]	87	17
Lawrence et al.[5]	15	47
O'Rourke et al.[6]	30	36
Willerson et al.[7]	27	11
Hochberg[8]	112	28
Total	296	

replacement. Two patients survived to be discharged although one died 3 months later after recurrence of congestive failure and an interventricular septal defect.

The five patients with crescendo angina include three with the classic criteria for preinfarction angina and two with enzyme and electrocardiographic evidence of acute myocardial infarction. Four of these survived.

Complications of intraaortic balloon pumping: Complications were most common in the group with cardiogenic shock. Serious arterial insufficiency developed in 7 of the 29 patients; in the group with shock, the rate of this complication approached 50 percent. Obstruction by the catheter, low cardiac output and intense vasoconstriction were common causative factors. Gangrene of both legs developed in two patients. Neither was a long-term survivor although one required bilateral amputation. Severe ischemic damage to the calf muscles of one leg occurred in another patient after a cardiac arrest during insertion of the balloon. This patient was a long-term survivor. In one case, the balloon was removed because of blanching and mottling of the leg; the patient did not survive. Another patient manifested temporary ischemia with blanching or mottling that did not require removal of the balloon. Complete occlusion of the superficial femoral artery was found in two patients at the time of balloon removal after prolonged pumping. The duration of pumping for the medical group was 1 to 10 days (average 4.75 ± 3.14 [standard error of the mean] days). Hemodynamic measurements during intraaortic balloon pumping revealed a significant elevation of diastolic pressure (55 mm Hg mean pressure) but an insignificant reduction of systolic pressure.

Surgical Group

In this group, the most common indication (34 cases) was inability to remove the patient from pump-oxygenator support at the end of heart surgery. Ten of the 34 patients with this indication (29 percent) died in the operating room, but 16 (47 percent) were long-term survivors. The prophylactic use of intraaortic balloon pumping in 17 patients with poor ventricular function, manifested by a low ejection fraction (average 0.29) and congestive heart failure (8 patients) resulted in only one death in this high risk group. Unsuccessful passage through the femoral artery occurred in seven patients (9 percent) although in four of these the balloon could be placed through a catheter in the aortic arch for later removal without thoracotomy.

Complications: Ischemic complications were less in the surgical than in the medical group (Table II). Gangrene did not occur. The balloon was removed prematurely in three patients because of arterial obstruction and ischemia of the leg without permanent damage. One of these patients died with cardiogenic shock. The balloon placed preoperatively for angina and acute myocardial infarction in two patients had to be removed immediately after operation because of intense vasoconstriction and circulatory obstruction. The balloon was reintroduced later in one patient when normal vascular tone returned. Other problems included iliac arterial obstruction due to distal displacement of the balloon, thrombus occlusion of the femoral artery and large hematoma of the thigh. In one patient the balloon was removed because previously existing aortic insufficiency was made worse. Cardiac tamponade secondary to anticoagulant therapy used with the balloon caused death in one patient.

Examination of the combined groups (Table III) reveals that in 13 percent the balloon could not be inserted through the femoral or iliac arteries, serious arterial occlusion occurred in 11.6 percent, and the total incidence rate of complications in the 86 patients in whom the balloon assist was used was 17.4 percent.

Discussion

The intraaortic balloon has found an increasing number of medical and surgical applications during the last 6 years. Survival under conditions of cardiogenic shock and post-pump oxygenator failure has been enhanced, and the results and operability of the poor risk patients with reduced ejection fraction, intractable angina and recent myocardial infarction have been improved. Although the salvage and benefits have been impressive there has been a significant incidence of failure to place the balloon by the femoral route and a correspondingly high rate of complications that restrict or eliminate the possible benefits for some patients.

Clinical results: The clinical results of intraaortic balloon pumping for cardiogenic shock without surgical intervention are quite variable and undoubtedly related

to the selection of patients. The survival rate with discharge from the hospital of 71 percent in our small group of 14 patients with shock is unusually high. Table IV reviews the experience in six studies with a total cumulative experience of 296 patients treated for cardiogenic shock. Survival with discharge from the hospital ranged from 18 to 47 percent and averaged about 26 percent. All groups were preselected by local indications that were often developed by trial and error and instinct. Definite criteria for identifying the high risk or unsalvageable patient are not available. Willerson et al.[7] reported that the ventricular volumes were abnormal and the ejection fraction less than 30 percent in all the patients with cardiogenic shock who underwent cardiac catheterization. This finding is in accord with clinicopathologic correlations demonstrating that patients who die with cardiogenic shock after acute myocardial infarction have more than 40 percent of the left ventricle destroyed by old or new infarction.[9,10] Some investigators[6] did not accept patients above age 65. The ability of intraaortic balloon pumping to improve collateral blood flow or prevent extension of the infarction, or both, is undoubtedly critical to the salutary results we have seen.[11,12] In our series each patient had hypotension not related to diminished preload. The majority had clinical congestive heart failure that was substantiated by the recording of elevated pulmonary capillary wedge pressure.

The results in surgical patients failing to tolerate removal of pump-oxygenator support at the end of the cardiac procedure are similar to those reported by others.[13,14]

Failure of balloon insertion: Failure to place the balloon by the femoral or iliac route is a serious limitation of the effectiveness of this technique. Our experience suggests a higher failure rate than is generally conceded. Hochberg[8] found in more than 400 case reports only 3 cases in which the balloon could not be passed. Page et al.[8] in a separate report found only 1 in 70 patients in whom they could not insert the balloon. In our medical group the failure to insert occurred in 16 percent of patients; all of these patients were over age 70. The failure of balloon passage in the surgical group would have been much higher than 4 percent if an alternative route through the aortic arch had not been available. The aortic arch graft is a valuable alternative since it makes possible removal of the balloon without a major thoracotomy and reduces the incidence of unsuccessful balloon passage during surgery to zero.

Complications: The incidence and nature of the complications of balloon pumping vary with the indication and the duration of use. Although aortic injury and dissection are often mentioned as possible sequelae,[15,16] they occur rarely, and only one patient in our series was thought to have such an injury. The most common and limiting complications involve the circulation to the legs and the integrity of the iliofemoral arteries. Perforation of the iliac artery has been known to occur during insertion. Arterial insufficiency requiring removal of the balloon, thrombectomy and possibly other procedures for revascularization were noted in 0 to 15 percent of the reported series.[5–8] Gangrene and ischemic damage to limbs have been reported as isolated instances,[2,5,8] usually under circumstances of shock and intense vasoconstriction. Loss of limb presupposes that the patient survives. The incidence of gangrene of the leg in the nonsurvivors is not known. One patient in our group required bilateral amputation above the knee. Two other patients would have required a similar procedure had they survived. Hochberg[8] found mention of two amputations, one above and one below the knee, in 386 case reports. Death as a direct result of intraaortic balloon pumping occurred in one of our patients and has been reported by others.[2] Infection was not one of the complications.

The complications are thought to be the result of diseased arteries, low cardiac output and the limitations of current technology. Outside the operating room the balloons were all placed by senior surgeons in the surgical or cardiac intensive care units who used standard techniques. No complication could be ascribed to faulty technique. We believe that judicious use of dextran and heparin with sensitive tests for controlling anticoagulation levels will help prevent most cases of thrombosis. However, in the postoperative patient, chest and pericardial drainage tubes should be in place during anticoagulation to prevent tamponade. Prompt thrombectomy and, if necessary, removal of the balloon have restored limb circulation and viability in most cases when difficulty has been recognized early. The addition of Doppler monitoring of circulation should provide greater critical observation and increase safety. Finally, some femoral or iliac arteries should not be cannulated because they are too small for the proposed cannulas.

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Acute Effects of Glucose-Insulin-Potassium Infusion on Myocardial Substrates, Coronary Blood Flow and Oxygen Consumption in Man

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To determine whether myocardial oxygen consumption (MVO_2) might be reduced when myocardial substrate uptake is changed from predominantly lipid to predominantly carbohydrate, measurements of arterial-coronary sinus glucose, lactate, free fatty acids, oxygen, carbon dioxide and coronary sinus blood flow (by thermodilution) were obtained in 13 fasting patients. Measurements were initially made in a basal control state and then repeated at 10, 20 and 30 minutes during an infusion of glucose-insulin-potassium. After 30 minutes of infusion, there was a three-fold increase in myocardial glucose uptake (44 ± 10 to 145 ± 19 μmoles/min [mean ± standard error of the mean], $P < 0.01$), a two-fold increase in myocardial lactate uptake (35 ± 4 to 77 ± 10 μmoles/min, $P < 0.001$) and a 75 percent decrease in myocardial free fatty acid uptake (34 ± 5 to 9 ± 3 μmoles/min, $P < 0.01$). Cardiac respiratory quotient rose from 0.70 ± 0.05 to 0.93 ± 0.08 ($P < 0.001$). Sum of oxygen extraction ratios for glucose and lactate rose from 51 ± 7 percent at control to 155 ± 22 percent at 30 minutes of infusion ($P < 0.001$) and suggested that much of the enhanced myocardial carbohydrate uptake met a nonoxidative fate, such as glycogen formation. During glucose-insulin-potassium infusion, arterial-coronary sinus oxygen decreased by 13 percent, coronary sinus blood flow increased by 12 percent and MVO_2 was unchanged. The increase in coronary sinus blood flow was associated with a 13 percent decrease in coronary vascular resistance and a small, but significant, increase in serum osmolarity (289 ± 3 to 299 ± 3 mOsm/liter, $P < 0.001$).

It is concluded that glucose-insulin-potassium infusion, while causing prompt alteration in myocardial substrate utilization from lipid to carbohydrate, produces no significant measurable change in myocardial oxygen consumption. However, such infusion is accompanied by a measurable increase in coronary sinus blood flow and a decrease in coronary vascular resistance.

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Glucose-insulin-potassium infusion was introduced clinically by Sodi-Pallares et al.[1] as a potential means of reducing the arrhythmic complications of acute myocardial infarction. Subsequent clinical trials[2–6] have yielded conflicting data on its ability to modify the mortality and morbidity of acute myocardial infarction. Renewed interest in glucose-insulin-potassium has been generated by recent studies of Maroko et al.,[7] demonstrating a reduction in myocardial infarct size in dogs during its infusion, and by studies of Opie et al.,[8,9] showing preservation of tissue glycogen and high energy phosphate with glucose-insulin-potassium in baboon and canine myocardial infarct models.

Relatively little data are available on the effects of glucose-insulin-potassium infusion on myocardial metabolism in human beings. In a

previous report,[10] we have shown that such infusion in patients with stable coronary artery disease is associated with enhancement of myocardial carbohydrate utilization, reduction of myocardial free fatty acid utilization and reduction of myocardial arteriovenous oxygen difference. Although we did not measure coronary blood flow in that study, we postulated that myocardial oxygen consumption might have decreased in conjunction with the glucose-insulin-potassium infusion.

This study was undertaken to investigate further whether myocardial oxygen consumption is altered by infusion of glucose-insulin-potassium in patients in stable condition undergoing cardiac catheterization. We will show that, despite the previously described decrease in myocardial arteriovenous oxygen difference during such infusion, there is an equivalent simultaneous increase in coronary sinus blood flow, resulting in an unchanged myocardial oxygen consumption. We will show that this alteration in coronary sinus blood flow is a consequence of reduced coronary resistance and will propose mechanisms for this altered coronary resistance.

Methods

Patient population: After giving informed consent, 13 men with a clinical history suggestive of ischemic heart disease underwent diagnostic cardiac catheterization (Table I). All patients fasted for 12 hours before catheterization and received no premedications. After completion of the metabolic protocol to be described, all patients underwent selective coronary angiography and biplane left ventriculography. Angiographic data (Table I) show that 10 of the 13 patients were found to have significant coronary artery disease. Quantitative angiographic measurements (Table I) were determined as previously described.[11] All 13 patients had normal findings on a 3 hour glucose tolerance test.

Metabolic protocol: All patients remained pain-free and in a state of stable equilibrium throughout the study. A small polyethylene catheter was inserted percutaneously into the right brachial artery using the Seldinger technique and advanced to the central aorta. A left antecubital vein was isolated, and a specially designed no. 7 or 8F catheter (Wilton Webster Manufacturing Company, Altadena, California, models CCS-7U-90A and CCS-8U-90B) was positioned in the coronary sinus for sampling of coronary sinus metabolites and for measurement of coronary sinus blood flow by thermodilution. The catheter position within the coronary sinus was verified with oximetry. The position of the catheter in relation to skeletal landmarks and to other catheters was noted, and great care was taken to maintain the stability of catheter position throughout the study. A no. 7F Goodale-Lubin catheter was introduced percutaneously by the right femoral venous route into the right atrium. The patency of each of the catheters was maintained with 0.9 molar saline solution. Heparin was not used.

TABLE I

Clinical and Angiographic Data

Patient no.	Age (yr)	Chol	Tg	CAD	EF
1	54	258	295	3v	0.40
2	37	221	151	3v	0.28
3	58	174	88	1v	0.43
4	51	224	182	2v	0.58
5	45	201	104	2v	0.38
6	32	376	233	3v	0.54
7	46	249	216	1v	0.44
8	38	239	302	1v	0.29
9	48	205	94	NI	0.69
10	39	204	143	2v	0.68
11	64	310	207	NI	0.72
12	43	192	127	1v	0.43
13	35	194	124	NI	0.45

CAD = coronary artery disease listed as number of vessels (v) with 70 percent or greater stenosis; Chol = cholesterol (mg/100 ml); EF = ejection fraction; NI = normal; Tg = fasting serum triglyceride (mg/100 ml).

After catheter placement, control measurements were made of aortic pressure, heart rate, coronary sinus blood flow, serum osmolarity and arterial-coronary sinus oxygen content, carbon dioxide content, glucose, free fatty acids, lactate, potassium and pH. A bolus dose of 10 g of glucose and 5 units of regular insulin was then injected into the right atrial catheter, and a continuous infusion was begun of glucose-insulin-potassium (300 g of glucose, 50 units of regular insulin and 80 mEq of potassium per liter) at 0.033 ml/kg per min (2 ml/kg per hour). This solution had an osmolarity of 1,827 mOsm/liter and a pH of 4.5. The baseline measurements were then repeated at 10 minute intervals for the next 30 minutes.

Assay techniques: *1. Aortic pressure* was measured with a Statham P23Gb strain gauge (Statham Instruments, Inc., Oxnard, California) with reference level at 10 cm above table top, and pressure was recorded on a photographic recorder (Electronics for Medicine DR-8 recorder).

2. Coronary sinus blood flow was determined with a computerized modification of the technique of Ganz et al.,[12] using room temperature 0.9 molar NaCl saline solution injected at a rate of 36 ml/min. All flow determinations were performed in duplicate, and the reproducibility of repeat determinations was 4.0 percent (mean of differences).

3. Chemical determinations: a. Oxygen and carbon dioxide content were determined with the method of van Slyke and Neill.[13] In our laboratory, coefficients of variation are less than 0.5 percent for these determinations.

b. Metabolic substrates: 1. Glucose and free fatty acids: Blood was collected in chilled tubes containing sodium ethylenediaminetetraacetic acid (EDTA) to prevent clotting. Blood was assayed for glucose with the glucose oxidase method of Washko and Rice[14] and expressed as μmoles glucose/liter whole blood. Free fatty acids were analyzed with the method of Itaya and Ui[15] and expressed as μmoles/liter plasma. Coefficients of variation for the glucose and free fatty acid assays in our laboratory are 1 percent and 5 percent, respectively.

2. Lactate: Immediately upon its withdrawal from the patient, 2 ml of blood was added to 6.5 ml of 6 percent perchloric acid. The tubes were weighed before and after addition of the blood to determine the exact amount added. Tubes were then centrifuged at 6000 × *g* for 30 minutes to remove the precipitated protein. The perchloric acid extract was titrated to pH 4.5 with 1 molar potassium hydroxide at 0° C with agitation. Thirty minutes later, precipitated potassium perchlorate was removed from the mixture by centrifugation at 6000 × *g* for 15 minutes. The supernatant was then assayed for lactate spectrophotometrically by the method of Hohorst[16] and expressed as μmoles lactate/liter whole blood. The coefficient of variation for lactate analysis is 3 percent in our laboratory.

3. Miscellaneous: Osmolarity was determined by freezing-point depression with an Osmette Precision osmometer,

model no. 2007 (Precision Systems, Sudbury, Massachusetts). Blood pH was determined using a Radiometer BMS3 pH meter with PHM72 digital acid-base analyzer (Radiometer, Copenhagen, Denmark). Serum potassium was assayed using a model 143 IL Instruments flame photometer (Boston, Massachusetts).

Calculations: *1. Coronary vascular resistance* (CVR) was expressed in (mm Hg)/(ml/min):

$$CVR = MAP/CSBF$$

where MAP is mean aortic pressure in mm Hg and CSBF is coronary sinus blood flow (ml/min).

2. Myocardial respiratory quotient (*RQ*) was expressed as:

$$RQ = (A\text{-}CS\ CO_2)/(A\text{-}CS\ O_2)$$

where A-CS CO_2 is arterial-coronary sinus carbon dioxide difference (ml/100 ml blood) and A-CS O_2 is arterial-coronary sinus oxygen difference (ml/100 ml blood). Normal values for myocardial respiratory quotient range from 0.70 for pure fat oxidation to 1.00 for pure glucose oxidation; intermediate values normally suggest combinations of fat and glucose oxidation.[17]

3. Myocardial oxygen consumption (MVO_2) was determined in ml/min:

$$MVO_2 = (A\text{-}CS\ O_2) \times (CSBF) \times 100$$

Equations for determination of MVO_2 and "consumption" of the other substrates listed are predicated on the assumptions that coronary sinus blood flow is representative of coronary arterial blood flow,[12] and that the arterial-coronary sinus difference adequately reflects net myocardial uptake or release of a given substrate. Patients with coronary artery disease often have inhomogeneous patterns of regional metabolism and regional blood flow,[18] but because each patient in this study served as his own control, we believe that valid comparisons with the control state can be made after the intervention (glucose-insulin-potassium infusion).

4. Myocardial uptake of glucose, free fatty acids, lactate and potassium was determined as the product of the arterial-coronary sinus difference for each substance and coronary sinus blood flow.

5. Lactate extraction was defined as the ratio of arterial-coronary sinus lactate to arterial lactate, expressed as percent.

6. Oxygen extraction ratio (*OER*) of a given myocardial substrate was defined as that percent of the myocardial oxygen consumption that could be accounted for if that substrate were completely oxidized. The formula was as follows[19–21]:

$$OER\ (\%) = \frac{(A\text{-}CS\text{-}S)(O_2Eq\text{-}S)}{(A\text{-}CS\ O_2)} \times 100$$

where A-CS-S is arterial-coronary sinus difference for a given substrate, A-CS-O_2 is arterial-coronary sinus difference for oxygen and O_2 Eq-S is oxygen equivalent for substrate S (free fatty acids 24.5, glucose 6, lactate 3).

7. Statistics: Data are reported as mean ± standard error of the mean. The paired *t* test was used to assess differences between paired data.

TABLE II

Hemodynamic and Metabolic Sequelae of Glucose-Insulin-Potassium (GIK) Infusion

	Control Period	Minutes of GIK Infusion		
		10	20	30
Heart rate (min^{-1})	67 ± 2	70 ± 3†	73 ± 3‡	73 ± 3*
Mean aortic pressure (mm Hg)	85 ± 3	81 ± 4*	81 ± 3	82 ± 3
CS blood flow (ml/min)	146 ± 12	164 ± 16*	164 ± 16*	163 ± 16*
Coronary vascular resistance (mm Hg)/(ml/min)	0.62 ± 0.05	0.53 ± 0.05‡	0.53 ± 0.04†	0.54 ± 0.05*
Arterial pH	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
CS pH	7.34 ± 0.01	7.33 ± 0.01†	7.32 ± 0.01†	7.32 ± 0.01*
Arterial osmolarity (mOsm/liter)	289 ± 3	298 ± 4*	298 ± 3‡	299 ± 3‡
Arterial O_2 (ml/100 ml)	17.9 ± 0.5	17.4 ± 0.5†	17.1 ± 0.5‡	17.2 ± 0.5†
A-CS O_2 (ml/100 ml)	11.2 ± 0.4	9.8 ± 4‡	9.6 ± 0.4‡	9.9 ± 0.3‡
MVO_2 (ml/min)	16.4 ± 1.4	16.3 ± 1.7	16.0 ± 1.7	16.1 ± 1.5
Arterial glucose (μmoles/liter)	4720 ± 230	9660 ± 350‡	9310 ± 360‡	8730 ± 410‡
A-CS glucose (μmoles/liter)	303 ± 61	949 ± 172†	893 ± 119‡	872 ± 136†
Myocardial glucose uptake (μmoles/min)	44 ± 10	154 ± 32†	142 ± 21†	145 ± 19†
Arterial lactate (μmoles/liter)	944 ± 86	1142 ± 97†	1460 ± 89‡	1797 ± 100‡
A-CS lactate (μmoles/liter)	253 ± 34	330 ± 68	414 ± 61†	504 ± 67‡
Myocardial lactate uptake (μmoles/min)	35 ± 4	46 ± 8	62 ± 11*	77 ± 10‡
% lactate extraction	27 ± 4	27 ± 4	28 ± 4	28 ± 3
Arterial FFA (μmoles/liter)	478 ± 41	352 ± 37†	259 ± 29‡	214 ± 22‡
A-CS FFA (μmoles/liter)	236 ± 32	118 ± 25†	82 ± 15†	55 ± 18‡
Myocardial FFA uptake (μmoles/min)	34 ± 5	20 ± 5*	12 ± 3†	9 ± 3†
Arterial K^+ (mEq/liter)	4.1 ± 0.1	3.7 ± 0.1‡	3.6 ± 0.1‡	3.7 ± 0.1‡
A-CS K^+ (mEq/liter)	0.1 ± 0.1	0.0 ± 0.1	0.0 ± 0.1	0.1 ± 0.1
Myocardial K^+ uptake (mEq/min)	0.02 ± 0.01	0.00 ± 0.01	0.00 ± 0.01	0.02 ± 0.01
Cardiac respiratory quotient	0.70 ± 0.05	0.83 ± 0.04†	0.90 ± 0.03‡	0.93 ± 0.08‡
Oxygen extraction ratios (%):				
Glucose	36 ± 7	131 ± 22†	126 ± 17‡	121 ± 21†
Lactate	15 ± 2	24 ± 4*	30 ± 4†	35 ± 4‡
FFA	64 ± 7	40 ± 9*	27 ± 5†	17 ± 5†
Total	115 ± 8	200 ± 22†	183 ± 24*	172 ± 21*

* $P < 0.05$ (versus control).
† $P < 0.01$ (versus control).
‡ $P < 0.001$ (versus control).
A-CS = arterial-coronary sinus difference; CS = coronary sinus; FFA = free fatty acids; Glu = glucose; K^+ = potassium; MVO_2 = myocardial oxygen consumption; O_2 = oxygen.

Results

The hemodynamic and metabolic sequelae of glucose-insulin-potassium infusion are summarized in Table II and displayed graphically in Figures 1 to 3. Because all patients remained in a state of stable equilibrium throughout the study, without evidence of chest pain or myocardial lactate production, data from the patients with coronary artery disease and from those with normal coronary arteries were analyzed together.

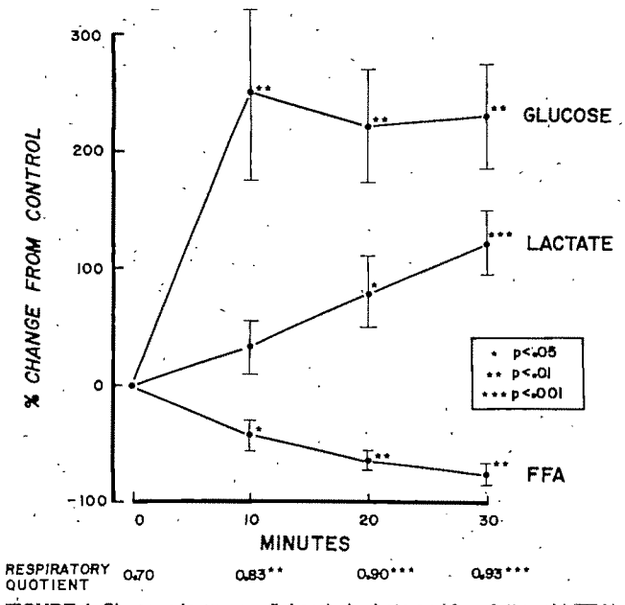


FIGURE 1. Changes in myocardial carbohydrate and free fatty acid (FFA) uptake during 30 minutes of glucose-insulin-potassium infusion. Shift to carbohydrate metabolism was manifest by a significant elevation in myocardial glucose and lactate uptake, decrease in free fatty acid uptake and increase in myocardial respiratory quotient. p = probability.

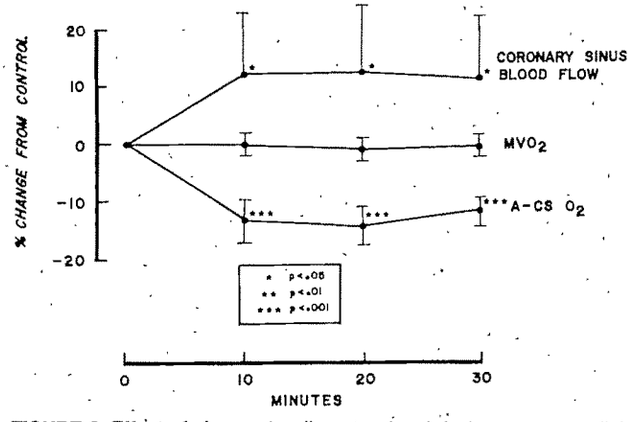


FIGURE 2. Effect of glucose-insulin-potassium infusion on myocardial oxygen consumption (MVO_2). During infusion, arterial-coronary sinus oxygen difference (A-CS O_2) decreased significantly, coronary sinus blood flow increased and MVO_2 remained unchanged; p = probability.

Myocardial energy substrates: There was a highly significant and sustained elevation of arterial glucose 10, 20 and 30 minutes after the administration of the glucose-insulin bolus injection and onset of glucose-insulin-potassium infusion (Table II). There was a concomitant three-fold increase in arterial-coronary sinus glucose and myocardial glucose uptake (Fig. 1). Arterial lactate, arterial-coronary sinus lactate and myocardial lactate uptake increased progressively, but more slowly, after commencement of infusion. Percent lactate extraction by myocardium remained unchanged, despite the two-fold increase in lactate utilization.

Arterial free fatty acid was reduced progressively during the 30 minutes of glucose-insulin-potassium infusion, with a corresponding decrement in arterial-coronary sinus and myocardial free fatty acid uptake. As additional evidence of the conversion from predominantly lipid to predominantly carbohydrate metabolism, the myocardial respiratory quotient rose from 0.70 ± 0.05 to 0.93 ± 0.08 ($P < 0.001$) during infusion.

Oxygen extraction ratios (Table II) in the control period suggested that free fatty acid oxidation accounted for the majority of the myocardial oxygen utilization. During glucose-insulin-potassium infusion, free fatty acid oxygen extraction ratio was dramatically reduced (64 ± 7 percent in control period to 17 ± 15 percent at 30 minutes, $P < 0.01$), and carbohydrate (glucose + lactate) oxygen extraction ratio was greatly increased (51 ± 7 percent in control state to 155 ± 22 percent at 30 minutes, $P < 0.01$). Oxygen extraction ratios totaling in excess of 100 percent during glucose-insulin-potassium infusion were compatible with a nonoxidative fate for glucose and lactate, such as myocardial glycogen or lipid formation.

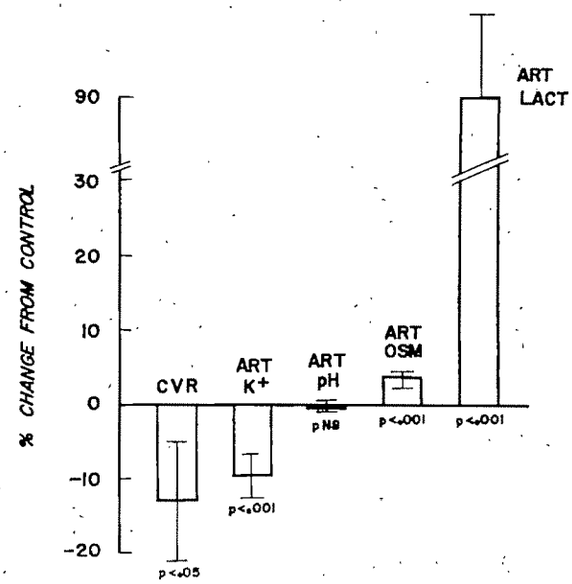


FIGURE 3. Changes at 30 minutes of glucose-insulin-potassium infusion in variables that might have altered coronary vascular resistance (CVR). ART = arterial; K^+ = potassium; OSM = osmolarity; LACT, = lactate; p = probability.

Myocardial oxygen consumption: Arterial-coronary sinus oxygen decreased abruptly, by 13 percent, when glucose-insulin-potassium was infused. However, because of a concomitant simultaneous and equivalent increase in coronary sinus blood flow, myocardial oxygen consumption showed no measurable change during infusion (Fig. 2).

Hemodynamic changes: There was a subtle, although significant, increase in heart rate associated with glucose-insulin-potassium infusion. Because mean aortic pressure did not increase, the increase in coronary sinus blood flow could not be explained by changes in coronary perfusion pressure, but could be explained by a decrease in coronary vascular resistance. Glucose-insulin-potassium infusion did not abnormally elevate right atrial pressure, which was 3 ± 1 mm Hg (range 0 to 6 mm Hg) at the end of the study period.

Determinants of coronary vascular resistance: Figure 3 summarizes the net change at 30 minutes of glucose-insulin-potassium infusion in several variables that may influence coronary vascular resistance: pH, osmolarity, arterial lactate and potassium. Arterial pH was unchanged; however, coronary sinus pH declined very slightly but significantly during infusion. Arterial serum osmolarity increased significantly, by 10 mOsm, during infusion. Arterial potassium decreased abruptly, by 0.4 mEq/liter, with the onset of infusion, but myocardial potassium uptake at 10, 20 and 30 minutes showed no significant changes from the control value.

Discussion

Background: Current interest in methods to reduce the size of myocardial infarcts has produced renewed enthusiasm for the use of solutions of glucose-insulin-potassium.[7–9,19] The theoretical benefits of this agent have recently been extensively reviewed[22,23] and include reduction of arrhythmias,[1,24–26] reduction of myocardial infarct size[7] and augmentation of myocardial contractility.[27] Proposed mechanisms of action of glucose-insulin-potassium are the following: restoration of myocardial intracellular potassium,[1,26,28] increase in glycolytic flux,[7,29] increase in serum osmolarity,[30,31] decrease in lysosomal activity,[32] acceleration of wound healing[33] and reduction of plasma free fatty acids.[6,8–10,34] Whether such treatment can actually improve survival of patients with acute myocardial infarction is controversial,[2–6] and no large, well controlled clinical trial has yet appeared.

In a previous study,[10] we showed that in patients with stable coronary artery disease glucose-insulin-potassium infusion enhanced carbohydrate uptake, reduced free fatty acid uptake and narrowed the arterial-coronary sinus oxygen difference. Although myocardial oxygen consumption was not measured, our data suggested that the infusion might have reduced oxygen consumption by altering myocardial metabolism from predominantly fat to predominantly carbohydrate oxidation.

Several lines of evidence are consistent with the hypothesis that glucose-insulin-potassium could reduce myocardial oxygen consumption by lowering free fatty acid levels. First, it is known that complete oxidation of fatty acids requires more oxygen per carbon unit than complete oxidation of carbohydrates.[35] Second, in the isolated rat heart, myocardial oxygen consumption was shown to be less when glucose rather than fatty acids was utilized as substrate.[36] Further, increased free fatty acid levels can increase myocardial oxygen consumption in the intact canine heart.[37] Finally, glucose-insulin-potassium infusion in dogs with experimental infarction[38] was shown to be associated with a reduction in myocardial free fatty acid uptake, an increase in glucose uptake and a reduction in myocardial oxygen consumption. On theoretical grounds, then, it can be argued that glucose-insulin-potassium might reduce myocardial oxygen consumption, perhaps by lowering elevated free fatty acid levels and replacing fat oxidation with carbohydrate oxidation. Such an effect would be applicable clinically both to the periinfarction ischemic zone of myocardium and to the central infarcting zone, where free fatty acid oxidation may continue, as shown in the dog heart infarct model.[39]

This study was performed to extend our previous observations on myocardial metabolism during glucose-insulin-potassium infusion in patients in stable condition undergoing cardiac catheterization, and, specifically, to determine if myocardial oxygen consumption is altered by such infusion.

Metabolic substrates: Observed alterations in myocardial lipid and carbohydrate metabolism after the intravenous bolus injection of glucose-insulin and the infusion of glucose-insulin-potassium (Fig. 1) were consistent with earlier findings reviewed by Bing[40] and Opie.[41] There was a prompt, sustained three-fold increase in myocardial glucose uptake, an apparently linear two-fold increase in myocardial lactate uptake and a 75 percent decrease in myocardial free fatty acid uptake after 30 minutes of infusion. Myocardial respiratory quotient reflected the switch from fat to glucose oxidation by its change from 0.70 ± 0.05 to 0.93 ± 0.08 ($P < 0.001$).

As previously discussed in detail,[10] the increased myocardial glucose uptake is probably related to the marked increase in arterial glucose levels and to the infusion of insulin, both of which facilitate transport of glucose across myocardial cell membranes.[42–44] Reduction of myocardial free fatty acid uptake may be secondary to reduced availability of this substrate related both to stimulation of extracardiac triglyceride synthesis by glucose-insulin-potassium[45–49] and to inhibition of free fatty acid release from adipose tissue.[50] The increase in myocardial lactate uptake was probably secondary to increased glucose availability with production of lactate from extracardiac sources, chiefly skeletal muscle and erythrocytes.[51]

Despite the two-fold increase in arterial lactate and myocardial lactate uptake, there was no change in arterial pH and only a small decline in coronary sinus pH (7.34 ± 0.01 to 7.32 ± 0.01, $P < 0.05$) after 30 minutes of glucose-insulin-potassium infusion. This is in contrast to studies on severely ischemic rat myocardium[52] that suggested that glucose and insulin infusions might

be detrimental through accumulation of lactate, reduction of pH and inhibition of intracellular enzymes. Our patients, however, despite the presence of coronary artery disease, probably had no significant resting myocardial ischemia because they were pain-free and without myocardial lactate production.

Oxygen extraction ratios (Table II): These ratios reflected the predominant free fatty acid oxidation in the control state, followed promptly by increased glucose and lactate oxidation as glucose-insulin-potassium was infused. Total oxygen extraction ratios during infusion were far in excess of 100 percent and likely indicated nonoxidative fates of the carbohydrates, such as glycogen synthesis or formation of alpha-glycerophosphate to be used in myocardial free fatty acid esterification; similar results were found[9] when glucose-insulin-potassium was infused in the canine infarct model. This indirect evidence for increase in glycogen stores in patients receiving glucose-insulin-potassium may be of considerable importance because enhanced intracardiac glycogen is hypothesized to be a major benefit of such infusion.[8,9]

Myocardial oxygen consumption: Although arterial-coronary sinus oxygen decreased significantly by 12 percent, there was a simultaneous 11 percent increase in coronary sinus blood flow during glucose-insulin-potassium infusion (Fig. 2); the product of these factors—myocardial oxygen consumption—showed no net change during infusion.

The significant increase in coronary sinus blood flow was unexpected and could not be explained by a change in mean coronary perfusion pressure, such as might be caused by an increase in mean aortic pressure, but rather by a significant decrease in coronary vascular resistance. Heart rate, a known determinant of myocardial oxygen consumption,[53] increased slightly with glucose-insulin-potassium infusion. No estimates of myocardial contractility, another major determinant of myocardial oxygen consumption,[54] were made in this study. Haneda et al.[38] found no change in contractility in their canine model during glucose-insulin-potassium administration under conditions of ischemia. However, Majid et al.[27] reported an increase in the first derivative of left ventricular pressure (dP/dt) during glucose-insulin-potassium infusion in man; similar studies[55] using catheter-tip manometry in our laboratory have recently confirmed this observation in patients in stable condition undergoing cardiac catheterization. Furthermore, glucose-insulin-potassium infusion in patients with acute myocardial infarction has recently been demonstrated by Mantle et al.[56] to improve left ventricular performance as assessed with serial left ventricular function curves.

Thus, in this study it is plausible that, despite the observed highly significant shift from fat to carbohydrate metabolism, the expected decrease in myocardial oxygen consumption was prevented by a glucose-insulin-potassium-mediated improvement in left ventricular inotropic state.

Coronary vascular resistance: Reduction of coronary vascular resistance with infusion of glucose-insulin-potassium has not previously been described, and the mechanism for this phenomenon is not unequivocally defined by our study. Mechanisms reported to reduce coronary vascular resistance include (1) increased serum potassium levels,[57–60] reduction of serum pH,[57,61–63] elevation of blood lactate,[57,64–66] and increased serum osmolarity.[67–69] Of these, only changes in lactate and osmolarity are of relevance to this study because arterial potassium did not increase and arterial pH remained unchanged during glucose-insulin-potassium infusion.

Lactate: Elliott et al.[66] reported that rapid fructose infusions in man produced a three-fold increase in myocardial lactate consumption, an increase in mean respiratory quotient from 0.66 to 0.81, an increase in coronary blood flow, a decrease in coronary vascular resistance and no change in myocardial oxygen consumption. Observed changes in coronary flow were attributed to vasodilating effects of lactate; osmolarity changes during the fructose infusion were not reported. Because, in our study, there was a two-fold increase in lactate consumption and directionally similar alterations in the other mentioned variables, it is likely that the mechanisms for increased coronary blood flow and decreased coronary resistance were similar, although it is conceivable that an increase in osmolarity, rather than lactate was the more important event in both studies.

Osmolarity: Infusion of glucose-insulin-potassium was associated with a significant 10 mOsm/liter elevation in serum osmolarity. Willerson et al.[67,68] recently showed that hypertonic mannitol infusion improves left ventricular performance and increases coronary blood flow in the experimental animal, and that mannitol administered to patients in a dose sufficient to increase serum osmolarity by 10 mOsm/liter results in increased left ventricular dP/dt, increased coronary blood flow and reduced coronary vascular resistance.[69] The precise mechanism linking increased osmolarity to coronary vasodilation is unknown. Thus the decreased coronary resistance observed in our study could be explainable on the basis of a small acute increase in serum osmolarity secondary to the initial glucose bolus injection and the sustained glucose-insulin-potassium infusion.

Clinical implications: Our data clearly show that glucose-insulin-potassium infusion in patients in stable, fasting condition is associated with a shift in myocardial metabolism from predominantly fat to predominantly glucose utilization, as previously reported.[10] Oxygen extraction ratios suggest that significant nonoxidative glucose metabolism (for example, glycogen synthesis) may begin promptly after glucose-insulin-potassium infusion. The data further indicate that, with infusion, myocardial oxygen consumption does not change significantly but coronary blood flow increases slightly as coronary vascular resistance decreases, perhaps secondary to an acute rise in serum osmolarity.

It should be noted that although most of our patients had ischemic heart disease, there was no clinical or metabolic evidence of ischemia during the study period. Consequently, our results cannot be immediately ex-

trapolated to acutely ischemic hearts without further investigation. Whether glucose-insulin-potassium might exert a salutary effect on coronary blood flow in patients with unstable manifestations of coronary artery disease is unknown, and the answer will await refinement of methods to assess regional coronary perfusion in patients with acute myocardial infarction. Indeed, it is conceivable that in patients with myocardial ischemia the diminished coronary vascular resistance secondary to glucose-insulin-potassium infusion could be potentially detrimental, producing a "coronary steal" phenomenon, shunting blood from ischemic to nonischemic tissue, as postulated for nitroprusside.[70]

We conclude that if glucose-insulin-potassium infusion is useful clinically to salvage ischemic myocardium, the mechanism is probably not related to decreased myocardial oxygen consumption secondary to the shift from lipid to carbohydrate metabolism. Other mechanisms discussed earlier, such as reduction of arrhythmias, reduction of plasma free fatty acids, increase in glycolytic flux, increased glycogen stores, enhancement of ventricular performance, decrease in lysosomal activity and acceleration of wound healing, are plausible mechanisms that warrant further clinical study.

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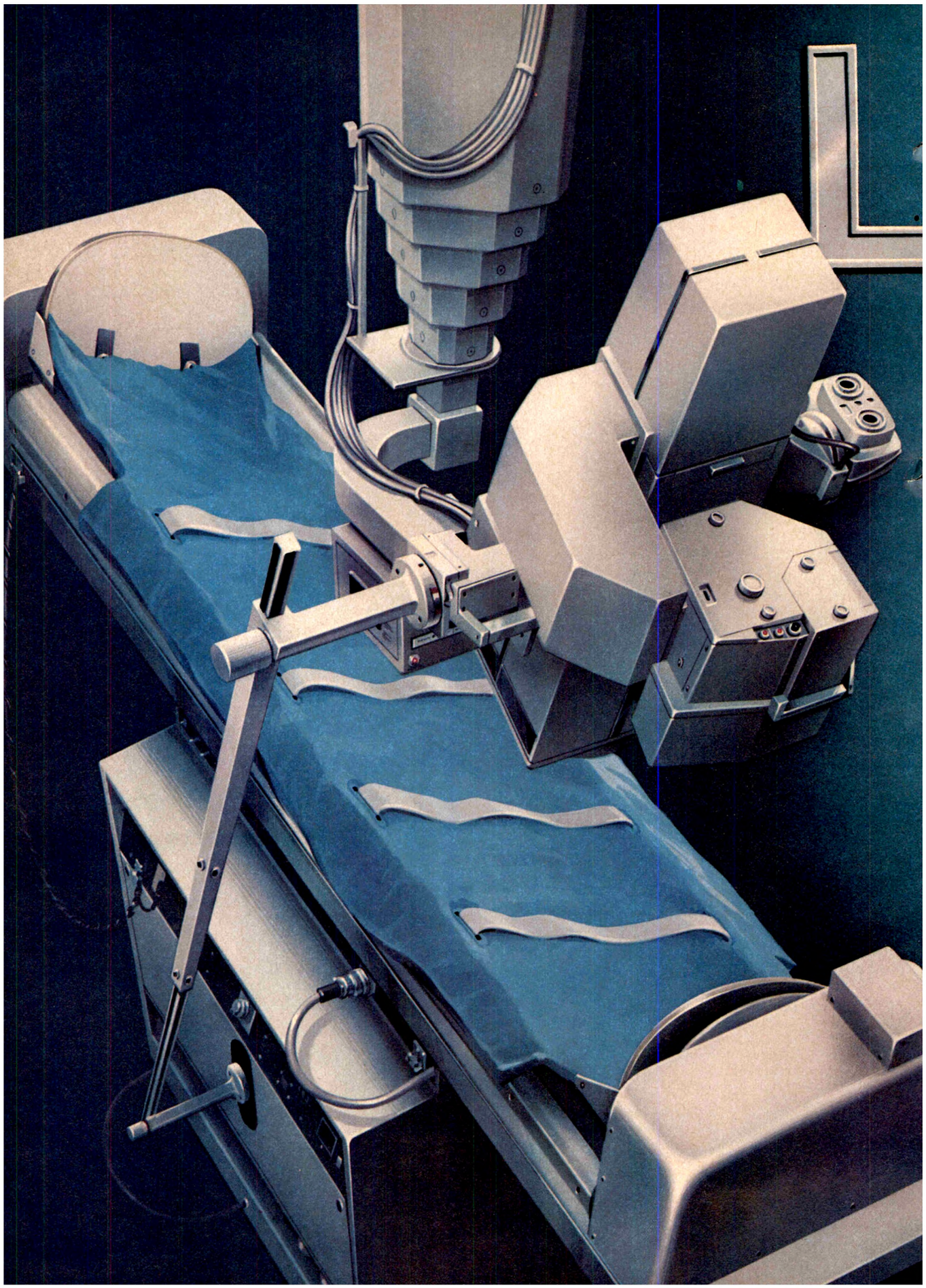
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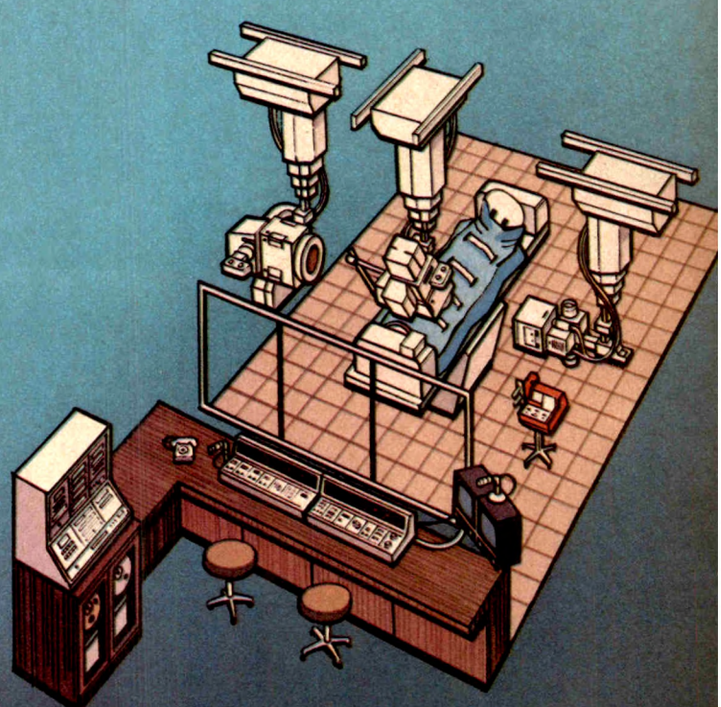
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Chart the
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in cholesterol
therapy.

Specific new approach to cholesterol lowering.

LORELCO is unrelated chemically to any other cholesterol-lowering agent presently available.

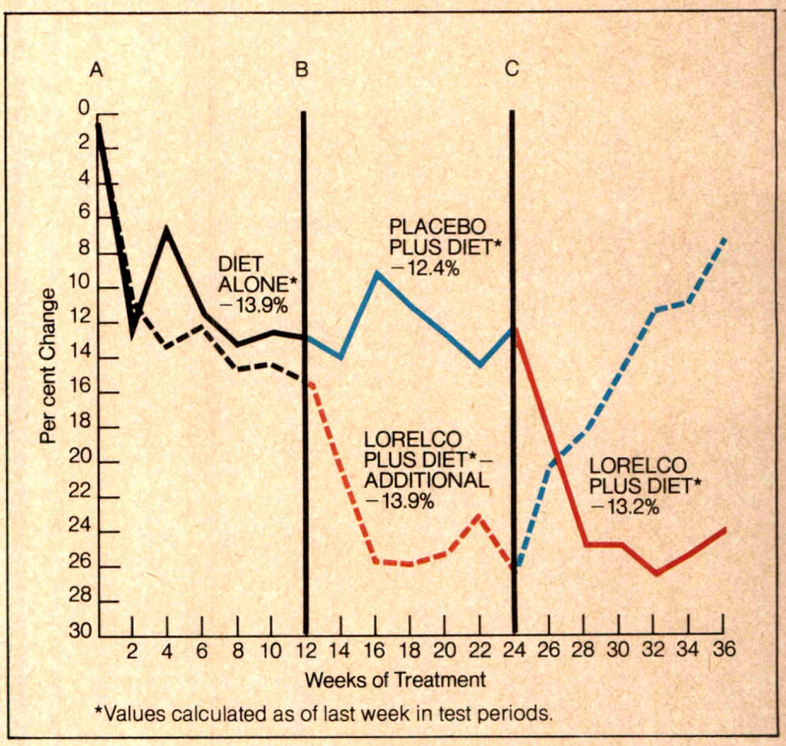
LORELCO, in combination with diet, yields significant reductions in serum cholesterol.†

As indicated in the figure at right:

☐ At point A, patients in two groups were placed on a diet low in cholesterol and saturated fat.

☐ At point B, one group of patients (red line) was started on therapy with LORELCO, two 250 mg. tablets twice daily, in addition to diet. Over the next 3 months, this group showed further reduction in serum cholesterol, significantly below that achieved with diet alone. The other group (blue line) received placebo while diet therapy was continued. No additional reduction in serum cholesterol levels was noted.

☐ At point C, the two groups were crossed over. Serum cholesterol levels increased rapidly when the group formerly receiving LORELCO was given placebo. Conversely, a sharp reduction in serum cholesterol occurred in the group given LORELCO instead of placebo.



†*J. LeLorier, S. Quidoz, S. Lussier-Cacan and J. Davignon, Clinical Research Institute of Montreal. Accepted for publication — Archives of Internal Medicine.*

Sustained reduction in serum cholesterol.

In long-term studies of 882 patients on various diets, regardless of fat or cholesterol content, 315 were maintained on LORELCO over a period exceeding four years. A significant reduction in mean serum cholesterol levels in that group was sustained throughout the study.

It's well-tolerated.

Diarrhea, the most common side effect occurred in about one patient in ten. Treatment was discontinued in about one patient in thirty because of side effects, mainly gastrointestinal disturbances.

It's convenient for your patients.

LORELCO offers convenient twice-a-day dosage. There's no noon-time dose to remember or forget. No inconvenient mixing or stirring.

Special note.

LORELCO is metabolized and excreted over a period of months. LORELCO is not recommended for use during pregnancy or in women contemplating pregnancy within 6 months.

LORELCO
PROBUCOL

Chart the course that's specific.

DOW

Dow Pharmaceuticals
The Dow Chemical Company
Indianapolis, Indiana 46268

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Current investigations now in progress may yield an answer to this question.

See complete product information on next page.

LORELCO
PROBUCOL

Chart the specific course in cholesterol therapy. 2 tablets b.i.d.

DESCRIPTION:
LORELCO (probucol) is an agent for the reduction of elevated serum cholesterol. The chemical name is 4,4'-(isopropylidenedithio) bis (2,6-di-t-butylphenol). Its chemical structure does not resemble that of any other available cholesterol-lowering agent. It is lipophilic.

CLINICAL PHARMACOLOGY:
The pharmacological mode of action by which LORELCO lowers serum cholesterol levels is unknown. However, there is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis it is concluded that LORELCO does not affect the later stages of cholesterol biosynthesis.

Absorption of LORELCO from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter, remain fairly constant.

At the end of 12 months of treatment in eight patients, blood levels averaged 19.0 μg/ml and ranged from 7.3 to 29.8 μg/ml. Six weeks after cessation of therapy, the average had fallen 60 per cent to 7.8 μg/ml (range from 3.2 to 16.3 μg/ml). After six months the average had fallen 80 per cent to 3.6 μg/ml (range from 1.5 to 6.0 μg/ml).

INDICATIONS AND USAGE:
Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long term use.

LORELCO is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins). LORELCO may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Current investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS (See also precautions):
LORELCO is contraindicated in patients who are known to have a hypersensitivity to it.

PRECAUTIONS:
Before instituting therapy with LORELCO an attempt should be made to control serum cholesterol by appropriate dietary regimens, weight reduction, and the treatment of any underlying disorder which might be the cause of the hypercholesterolemia.

Because LORELCO is intended for long-term administration, adequate baseline studies should be performed to determine that the patient has elevated serum cholesterol levels. Serum cholesterol levels should be determined frequently during the first few months of treatment and periodically thereafter. A favorable trend in cholesterol reduction should be evident during the first two months of probucol administration. The regimen should be followed as long as the trend continues. A decision should be made by the sixth month whether adequate reduction is being attained.

A baseline for serum triglycerides should also be established and serum triglyceride levels should be determined periodically. If a marked sustained rise in serum triglycerides is observed during probucol therapy, consideration should be given to improved diet compliance, alcohol abstinence, further calorie restriction or adjustment of carbohydrate intake. LORELCO (probucol) should not be continued if hypertriglyceridemia persists.

Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of LORELCO on serum cholesterol. The dosage of these agents is not usually modified when given with LORELCO.

Use in Pregnancy: Reproduction studies have been performed in rats and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to LORELCO. Because there are no adequate studies in pregnant women, use of this drug in pregnancy is not recommended. Furthermore, if a patient wishes to become pregnant, it is recommended that the drug be withdrawn, and birth control procedures be used for at least six months because of persistence of the drug in the body for prolonged periods. (See Clinical Pharmacology.)

Use in Nursing Mothers: It is not known whether this drug is excreted in human milk, but it is likely to be since such excretion has been shown in animals. It is recommended that nursing not be undertaken while a patient is on LORELCO.

Use in Children: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS:
The adverse reactions associated with LORELCO are generally mild to moderate and of short duration.

The most commonly affected system is the gastrointestinal tract. Diarrhea occurs in about one in 10 patients. Other adverse gastrointestinal reactions in descending order of frequency are: flatulence, abdominal pain, nausea and vomiting. These reactions are usually transient and seldom require the drug to be discontinued. During the clinical studies, LORELCO was discontinued in about 2 per cent of the patients because of adverse gastrointestinal reactions.

Less frequent adverse reactions are: hyperhidrosis, fetid sweat and angioneurotic edema which were reported in less than one in 500 subjects.

An idiosyncratic reaction characterized by dizziness, palpitations, syncope, nausea, vomiting and chest pain has been reported.

Other events have been reported in patients treated with LORELCO. The relationship between these events and probucol is not well established. In this group are included totally subjective complaints which are attributed to drugs even though many individuals have symptoms of this sort in the absence of drug ingestion. Also included are events which could have been produced by the patient's state or other modes of therapy. The most frequent were headaches, dizziness, paresthesias and eosinophilia observed in about one of each 50 subjects. Consistently low hemoglobin and/or hematocrit values were observed in about one of each 100 patients. Less frequent were: rash, pruritus, impotency, insomnia, conjunctivitis, tearing, blurred vision, tinnitus, diminished sense of taste and smell, enlargement of a multinodular goiter, anorexia, heartburn, indigestion, gastrointestinal bleeding, ecchymoses and petechiae, decreased hemoglobin, thrombocytopenia, nocturia, and peripheral neuritis. These were observed in the range of one to six per thousand subjects.

Elevations of the serum transaminases (glutamic-oxalacetic and glutamic-pyruvic), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen and blood glucose above the normal range were observed on one or more occasions in various patients treated with LORELCO. Most often these were transient and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between probucol and these abnormalities is not firm, the possibility that some of these are drug related cannot be excluded. In the controlled trials, the incidence of abnormal laboratory values was no higher in the patients treated with probucol than in the patients who received placebo.

DOSAGE AND ADMINISTRATION:
For adult use only. The recommended dose is 500 mg (2 tablets of 250 mg each) twice daily with the morning and evening meals.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:
Each film-coated tablet contains 250 mg probucol and is imprinted with the DOW diamond trademark over the code number 51.

Bottles of 120 tablets, a 30-day supply for one patient (NDC 0183-0051-26). Unit dose packages of 112 tablets (NDC 0183-0051-71).

Keep well closed. Store in a dry place, avoid excessive heat and dispense in light-resistant containers.

ANIMAL PHARMACOLOGY AND TOXICOLOGY:
From studies in rats, dogs and monkeys it is known that probucol accumulates slowly in adipose tissue. Approximately 90 per cent of probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body. After a single dose approximately 10 per cent of the absorbed drug was recovered from bile collected from rats over a period of 30 hours. Very little is excreted by way of the kidneys. Following a single intravenous injection in rats, only one per cent of the drug was recovered in the urine over a 24-hour period.

Probucol has shown no identifiable toxicity in mice, rats and monkeys. In mice and rats the LD_{50} (oral) is in excess of five grams per kilogram of body weight. Two-year chronic toxicity studies in rats and a study in monkeys exceeding seven years in duration have shown probucol to be without adverse effect.

During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles), there were 12 fatalities. The behavior, physical condition, laboratory findings and post-mortem evaluations were considered to be within normal limits.

Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine resulting in ventricular fibrillation in many dogs.

Among the animal species in which probucol has been studied, the dog is peculiar with respect to the phenomenon of sudden death and the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation. In other studies, monkeys were given probucol either before and after, or only after myocardial infarction induced by coronary artery ligation. In these studies there was no difference between probucol and placebo-treated groups with respect to either survival or detailed blind quantitation of myocardial changes (gross and histopathologic).

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

Probucol was administered to minipigs beginning 10 days before ligation of a coronary artery and continued for 60 days post surgery. Challenge with epinephrine at the end of 60 days failed to induce ventricular fibrillation in any of the coronary ligated, probucol-treated minipigs.

In summary, probucol is toxic to the dog; the target organ is the heart. This phenomenon appears to be unique to the dog. Toxic effects were not identified in four other species.

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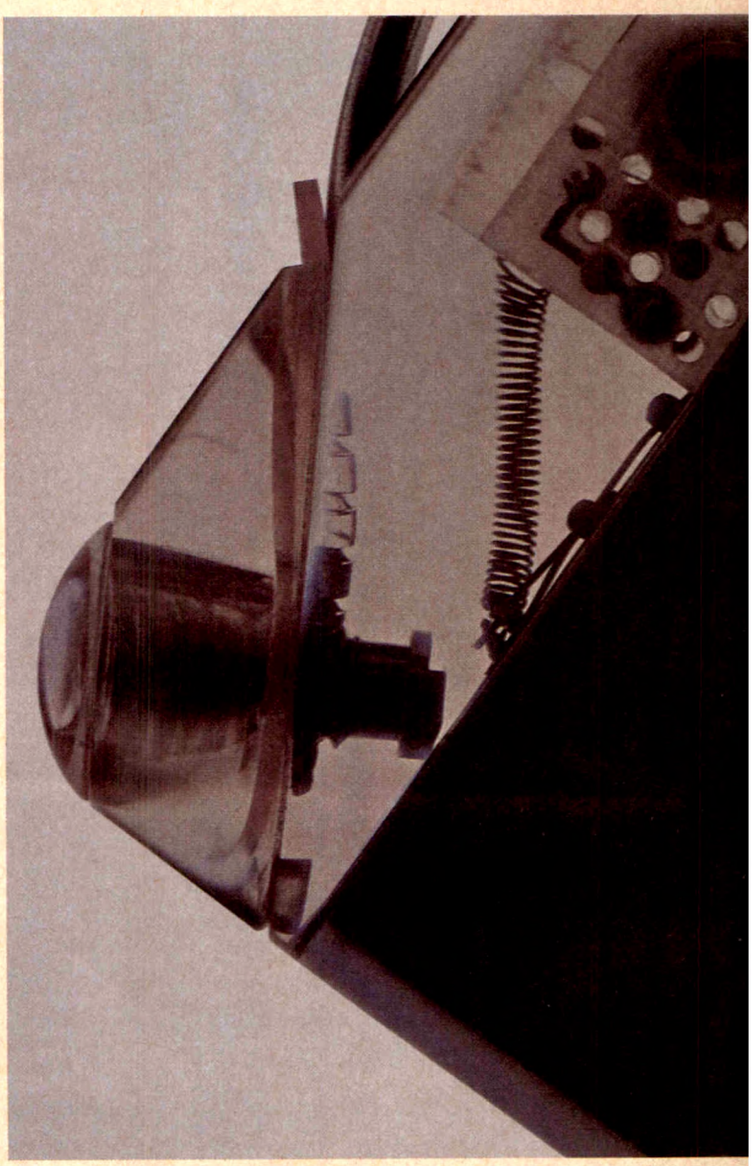
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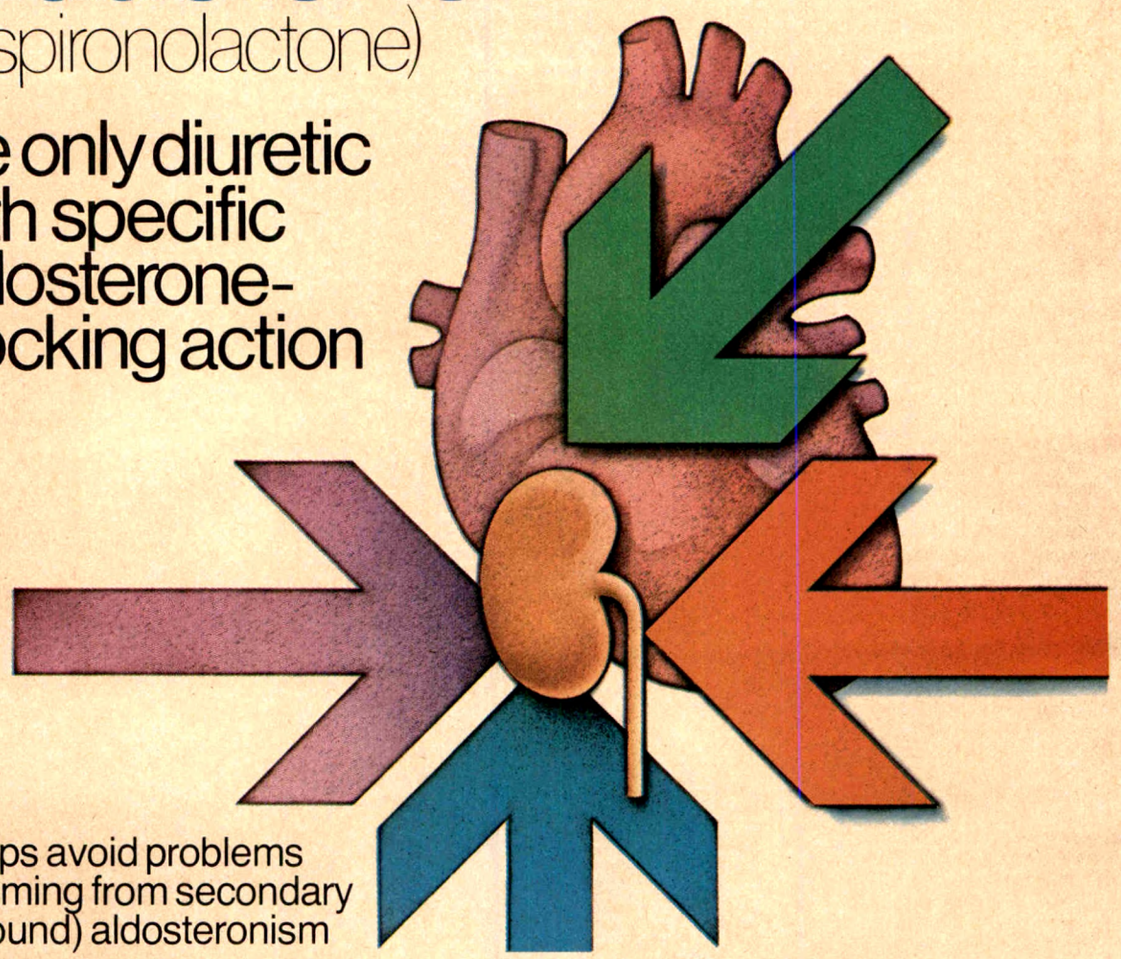
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*See the box *Warning* and the *Indications* section of the brief summary of prescribing information on opposite page. Before prescribing, please refer to the complete prescribing information.

†Indicated for the treatment of patients with hypokalemia, or for the prophylaxis of hypokalemia in patients taking digitalis, when other measures are considered inadequate or inappropriate.

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WARNING

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents: therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

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It's time for straight talk on the crux of the matter: the diagnostic image. Is it good or isn't it? If it isn't good *before* it gets to the TV screen, the monitor isn't going to improve it. And video disc of a bad image is like recording a football fumble: instant replay doesn't recover the ball.

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Less Is More

Caution: in a mobile image intensifier, bigger isn't necessarily better. Ask what those hefty specs mean. If they don't give you compactness, easy maneuverability, efficiency and the ability to get close to the patient quickly and precisely – then what you get only gets in your way.

Talk to us first about mobile image intensifiers. And about our unique fiber optics image intensification (you *may* want it on other Philips' diagnostic systems).

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Cardiac Rupture—Challenge in Diagnosis and Management

ROBERT J. BATES, MD*
STEVEN BEUTLER
LEON RESNEKOV, MD, FACC
C. E. ANAGNOSTOPOULOS, MD, FACC†

Chicago, Illinois

Previous studies of the incidence, natural history, pathogenesis and diagnosis of cardiac rupture are presented, and 20 additional cases described. Progressive cardiorrhexis after myocardial infarction causes death in possibly more than 25,000 persons a year in the United States, and more frequent antemortem diagnosis is needed. Suggestions for future clinical and experimental studies are described and possible means of early diagnosis and therapy are outlined.

"It seems then that a person dies from a broken heart, not in young adult life from a great grief or emotion, but usually in old age, on account of diseased coronaries. . . ."
Krumbhaar and Crowell, 1925[1]

Cardiorrhexis, or rupture of the heart, was first reported in 1647[2] and was described frequently in early studies.[1,3–7] Recent advances in the diagnosis and medical therapy of cardiac disease and improved techniques in cardiovascular surgery have suggested the need for a reexamination of this usually fatal but potentially treatable condition.

Among the many causes of death following acute myocardial infarction, free transmural rupture (cardiorrhexis) remains the most telling and often unanticipated complication. It is reported[8] to occur in up to 24 percent of fatal acute myocardial infarctions and, after cardiogenic shock and dysrhythmias, is the most important cause of sudden death after myocardial infarction.[9] Rupture of the wall of the heart is 8 to 10 times more common than rupture of a papillary muscle or the ventricular septum.[10,11] It remains the most common site of rupture in the cardiovascular system and is the most common cause of sudden hemopericardium in hospitalized patients.[12]

Although a major and almost universally fatal complication of myocardial infarction, cardiorrhexis remains a relatively unknown quantity. Controlled prospective studies are lacking and most published reports are anecdotal, representing the selective experience of particular investigators and institutions. Some efforts have been made to construct control populations from autopsy series,[13–16] but the true incidence in the population at large and in persons with a recent myocardial infarction remains in question. Its predisposing factors and causes have yet to be defined, and antemortem diagnosis is seldom made sufficiently early to permit effective therapy.

The development of modern coronary care units, the effective use of antiarrhythmic drugs and the increasingly successful mechanical support of patients with cardiogenic shock should tend to make cardiac rupture a more commonly observed incident as more individuals survive the initial insult of acute myocardial infarction.[9,17,18] In light of the rapid advances made in cardiac surgery and cardiology, in this report we (1) review the current literature on 1,200 cases of cardiac rupture, and add 20 autopsy-proved cases of our own, (2) suggest that the condition is more common than presently thought, (3) indicate that it is potentially

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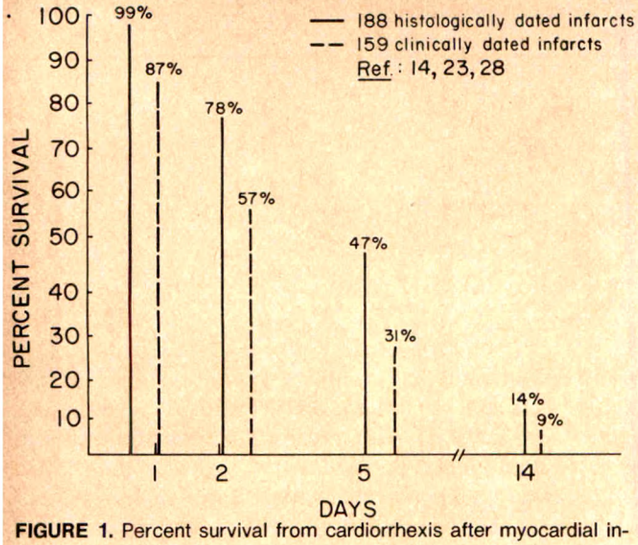


FIGURE 1. Percent survival from cardiorrhexis after myocardial infarction.

treatable, and (4) stimulate the development of new insight into the etiology, natural history, diagnosis and possible treatment of cardiorrhexis.

Review of Clinical Features

Pathogenesis

Causes: Although the most common cause of cardiac rupture is myocardial infarction,[19,20] other causes are infective endocarditis, myocardial abscess, dissecting aneurysm of the sinus of Valsalva, syphilitic myocarditis, tuberculosis, echinococcal cyst, trauma and malignancy.[21] In this review we shall confine the discussion to cardiac rupture as a complication of myocardial infarction.

Interval between infarction and rupture of the heart: Maher et al.[22] reported that more than 50 percent of ruptures occur during the first 5 days after infarction, and Lewis et al.,[23] using the histologic criteria of Mallory et al.[24] to estimate infarct age, reported that 22 percent occur within 24 hours of infarction. Similar time distributions have been observed using clinical criteria.[25–30] Other investigators have reported that rupture occurs infrequently before the 3rd[31] or 5th day.[32,33] Rupture occurring more than 2 weeks after the initial symptoms probably represents a superimposed infarction,[34–37] rupture through a false aneurysm[38–43] or, less commonly, a true aneurysm.[11,44,45]

A distinction should be drawn between the histologic and clinical estimates of the interval between infarction and rupture; several investigators[7,14,23,28] noted only a variable amount of agreement between histologic and clinical estimates. Possible explanations for discrepancies may include uncertainty about the clinical dating of acute myocardial infarction, the existence of "silent" myocardial infarction, confusion between initial and recurrent infarction or extension of infarction and, finally, confusion between myocardial infarction and the initial episode of cardiac rupture.[11,28,34,35] In terms of percent survival, after clinical or histologic onset of infarction, however, Figure 1 shows that only 50 percent or less of patients who eventually die of rupture do so within 5 days of onset of infarction.

In our series (Table I), clinical criteria were sufficient in 16 of 20 cases to estimate the interval between infarction and rupture. In 50 percent of cases, rupture occurred within 4 days and in 87 percent by 14 days (range less than 1 day to 21 days).

Appearance, size and location of rupture: Cardiac rupture does not usually occur by means of a ventricular "blowout," nor is the rupture uniform in appearance. The ruptures are variable and may appear as ragged, gaping, linear or three-cornered rents. The pathway of the rupture through the myocardium is most often circuitous and hemorrhagic. The endocardial opening is usually decidedly smaller than its epicardial counterpart, which ranges from 2 mm[37] to 3 cm.[15]

More than 90 percent of ruptures occur through the left ventricle. Most reports indicate that the anterior wall is most commonly involved,[21,23,27,29,46] but the distribution varies and in some series there is an equal distribution between anterior, posterior and lateral walls[11,13,14] or usually a predilection for the posterior wall.[15] In our series, 35 percent of ruptures occurred through the anterior wall, 35 percent through the posterior wall and 20 percent through the lateral wall; 10 percent occurred at the apex.

The proximity of the site of free cardiac rupture to the septum has been analyzed in several series.[13,14,23,29] It has been postulated that an association may be the result of muscle contracting with different force vectors over an area of weakened myocardium, which would then represent a "stress point" and be likely to rupture.[20,22,23,27,29,30,36]

There does appear to be a greater incidence of rupture of the lateral wall relative to the smaller incidence of infarction in this region.[11,47] The location of the origin of two papillary muscle groups on the lateral wall and the resulting increased stress could be a possible explanation for this finding.

Wessler et al.[15] found no correlation between the size of the infarction and the incidence of rupture, but Edmondson and Hoxie[31] thought that smaller infarcts have a greater tendency to rupture. Others[23,26,48–51] noted that rupturing infarcts tended to be large and extended over more than one circumferential zone of the ventricle. In our series, 60 percent of the ruptured infarcts were described as "massive."

Mechanism of rupture: The degree and extent of myocardial necrosis and the presence of a large neutrophilic granulocytic infiltrate are thought by some to be important etiologic factors in cardiac rupture. Ross and Young[13] compared the degree of polymorphonuclear infiltrate in patients who died of rupture before the 5th day after infarction and in control subjects who died of other complications of acute myocardial infarction. The patients with rupture had a greater degree of infiltration. Later, Lewis et al.[23] were unable to confirm this finding.

Lunseth and Runwaldt[51] analyzed 26 cases of cardiac rupture and found 8 in which myocardial degeneration

TABLE I

Twenty Cases of Autopsy-Proved Cardiac Rupture

Case no.	Age (yr) & Sex	Hyper-ten-sion*	Site & Size of Infarct	Site & Size of Rupture	Interval From Clinical Onset to Rupture (days)	Coronary Arteriosclerosis	Coronary Thrombosis	Previous Infarct	Dia-betes
1	73M	No	Distal 2/3 anterior wall LV and septum: "mas-sive"	Lateral wall LV: 7 cm	5	Severe LAD	LAD	Yes	No
2	58M	Yes	Anterior and posterior LV: "massive"	Lateral wall LV: 5 cm	8	Severe, generalized	LCA	No	No
3	76M	Yes	Posterior LV and RV	Posterior RV and septum: 2 cm	Dead on arrival	Severe, generalized	RCA	No	No
4	69M	Yes	Anterior wall RV, posterior wall LV	Anterior RV: 2 cm	5	Severe, generalized	Posterior circum-flex artery	No	. . .
5	70M	Yes	Anteroseptal LV: "massive"	Anterior LV near septum: 5 cm	21	Severe, generalized	None	Yes	No
6	65M	No	Anterior LV: "massive"	Anterior LV: 3 cm	19	Severe, generalized	LAD	No	. . .
7	69M	Yes	Posterolateral LV: 3.5 X 2.5 cm	Posterolateral: 1.5 cm	3	Severe, generalized	None	No	. . .
8	67M	No	Posterior LV: "massive"	Posterior, near septum: 0.8 cm	Dead on arrival	Severe, generalized	RCA	No	. . .
9	74M	. . .	Lateral LV	Lateral LV	Dead on arrival	Severe, generalized	None	No	. . .
10	65M	Yes	Anteroseptal LV: "massive"	Anterior LV	14	Severe, generalized	LAD	Yes	No
11	60M	Yes	Posterior LV: "massive"	Posterior LV: 3 mm	3	Severe LAD	None	No	No
12	50M	No	Anteroseptal LV: "massive"	Anterior LV: 2 cm	11	Severe, generalized	LAD	No	No
13	65M	Yes	Anteroseptal LV: "massive"	Anterior LV: 1 cm	4	Severe, generalized	LCA	Yes	. . .
14	59M	No	Anterior LV	Apex LV: 2.7 cm	6 hours	LAD, RCA	No	No	No
15	79F	Yes	Anteroseptal LV and RV: "massive"	Apex RV: 0.25 cm	3	Severe, generalized	LAD	Yes	Yes
16	87F	No	Posterior LV: "massive"	Posterior LV	5	Severe, generalized	RCA	No	Yes
17	77F	Yes	Lateral LV: "massive"	Lateral LV: 0.5 cm	1	Severe, generalized	LCx	Yes	Yes
18	78F	Yes	Anteroseptal LV	Anterior LV: 1 cm	1	Severe, generalized	No	No	No
19	82F	Yes	Posterior LV	Posterior LV	3	Severe, generalized	No	Yes	Yes
20	80F	. . .	Posterior LV	Posterior LV	Dead on arrival	Severe LAD	LCx	No	. . .

*Hypertension at any time after clinical myocardial infarction.
LAD = left anterior descending coronary artery; LCA = left main coronary artery; LCx = left circumflex coronary artery; LV = left ventricle; RCA = right main coronary artery; RV = right ventricle; . . . = not known.

was barely detectable. They concluded that the pathologic change of major importance was not the degree of leukocyte infiltration, but rather the large intramural hematoma apparently dissecting through the myocardium which they found at the sites of many ruptures. The source of hemorrhage could not be accurately established but was thought to be intramural. Kamil et al.[53] suggested that intramyocardial blood vessels, stretched and torn during systole when the infarcted area bulged, might be the source of the hematoma. Lautsch and Lanks[28] also agree that cardiac rupture may be a progressive event with a small endocardial rent leading to hematoma formation.

O'Rourke[17] presented two cases of rupture in a series of 19 patients who had cardiogenic shock after myocardial infarction. In comparison with the group with cardiogenic shock alone after infarction, those with rupture had shock later and presented with obvious right as well as left ventricular failure. O'Rourke suggested that a gradual episodic course for cardiac rupture is similar to the clinical course of an arterial aneurysm in which lesser episodes of bleeding commonly occur before terminal massive rupture.

Coronary artery disease: Diffuse atherosclerosis and occlusion of the coronary artery supplying the site of cardiac rupture is found in virtually all cases although

TABLE II

Incidence of Cardiorrhexis Among Cases of Acute Fatal Myocardial Infarction

Source	Year	Cases of Fatal Myocardial Infarction (no.)	Cases of Cardiac Rupture	
			no.	%
Parkinson & Bedford[54]	1928	51	5	9.8
Levine[33]	1929	46	9	19.6
Bean[36]	1938	114	17	14.9
Mallory et al.[24]	1939	72	8	11.0
Edmondson & Hoxie[31]	1942	865	72	8.3
Friedman & White[52]	1944	105	10	9.5
Mintz & Katz[55]	1947	46	5	10.4
Wartman & Hellerstein[56]	1948	111	6	5.5
Selzer[57]	1948	95	8	8.4
Diaz-Rivera & Miller[58]	1948	53	5	9.4
Foord[59]	1948	264	33	12.5
Wang et al.[60]	1948	267	23	8.6
Howell & Turnbull[62]	1950	111	8	7.2
Zinn & Cosby[34]	1950	430	34	7.9
Oblath et al.[26]	1952	1,026	91	8.9
Wessler et al.[15]	1952	256	14	6.0
Waldron et al.[63]	1954	545	40	7.5
Goetz & Gropper[64]	1954	145	14	9.6
McDonnieal et al.[65]	1955	144	12	8.0
Maher et al.[22]	1956	183	21	11.5
Zeman & Rodstein[49]	1960	81	16	19.7
Griffith et al.[29]	1961	3,103	215	6.9
Spiekerman et al.[8]	1962	87	21	24.0
Ross & Young[13]	1963	606	43	7.0
Sievers[66]	1964	811	104	12.8
London & London[25]	1965	1,001	47	5.0
Sugiura et al.[50,68]	1968	129	17	15.0
Sahebjamin[67]	1969	933	37	3.8
Lewis et al.[23]	1969	1,228	106	8.6
Beutler[61]	1970	250	20	8.0
Meurs et al.[37]	1970	34	8	23.5
Gjol[16]	1972	440	51	12.0
Naeim et al.[14]	1972	989	44	4.0
Hammer et al.[69]	1972	47	7	15.0
Havig[30]	1973	122	14	11.5
Total		14,795	1,185	8.0

vessel disease may be limited to the terminal ramifications.[10] Severe atherosclerosis was present in 74 percent of our 20 cases. VanTassel and Edwards[11] found no tendency toward single vessel disease although others[13,14,20,29,31,36,43,44] have reported involvement predominantly in the left anterior descending coronary artery.

Recent coronary arterial occlusion occurs more commonly in patients with rupture than in those who die of other complications of acute myocardial infarction. In the series of Wessler et al.,[15] the incidence and number of old coronary occlusions were significantly less in ruptured hearts than in nonruptured control hearts. In our series, fresh coronary occlusion was judged responsible for the recent infarct in 53 percent of the 20 cases of rupture.

Fibrosis and previous infarction: Patients who die of cardiac rupture generally have lower incidence rates of fibrosis and previous infarction.[15,22,25,31,33,49] Wessler et al.[15] found that the pathway of the rupture always passed through the area of most recent infarction that was free of fibrosis. Old infarcts were demonstrated histologically in 35 percent of our patients.

Collateral circulation: The presence of collateral circulation to infarcts that eventually rupture has been reported to be minimal and less than that seen in cases without rupture. Wessler et al.[15] summarized the generally accepted circumstance thought necessary for cardiac rupture—an acute coronary occlusion resulting in a fresh transmural myocardial infarction with poor collateral circulation and absence of fibrosis in at least one area of the infarct.

Role of the false aneurysms in cardiac rupture: Rupture of the left ventricle usually results in fatal hemopericardium, but confinement by the pericardium may limit hemorrhage and result in the formation of a fibrotic false aneurysm. True aneurysms are more commonly formed, but they rupture only rarely.[42]

VanTassel and Edwards[11] found nine cases of false aneurysm in their autopsy series of 40 cardiac ruptures. This unusually large number was no doubt due to their selection process. The anatomic locations were equally distributed over the left ventricle. As can be expected, these patients had a considerably longer survival time (3 weeks to 6 years) after myocardial rupture than is usual. Using radiologic and electrocardiographic evidence (persistent S-T elevation in leads overlying the aneurysm), only three of the nine cases were diagnosed during life. Four of the nine died as a result of rupture of the false aneurysm. Of the three patients whose

rupture was diagnosed, one died awaiting operation; the remaining two patients were reported to have had successful excision of the false aneurysms. Because true aneurysms seldom rupture, it is important to differentiate the two types when an aneurysm is suspected and to treat false aneurysms in a more aggressive surgical manner. Ventriculograms are necessary to differentiate true from false aneurysms. The former have characteristically wide openings into the ventricular chamber whereas false aneurysms most often have a narrow neck leading into the fundus.[42]

The formation of false aneurysm lends support to the premise that cardiac rupture may be slowly progressive in development because it seems probable that slow erosion of the myocardium or minute leaking pathways rather than massive hemorrhage are required for its formation. The slow release of blood into the pericardial space may cause pericardial irritation and adherence of the parietal pericardium to the heart. Continued hemorrhage is then loculated, fibrinous organization of the thrombus occurs and an aneurysm forms. Rupture may occur anywhere but is most commonly found at or near the junction of the fibrous sac and the epicardium.

Incidence of Cardiac Rupture

Although the generally accepted incidence rate of cardiac rupture in hospitalized patients who die of acute myocardial infarction is thought to be 10 percent,[20] a review of reported cases (Table II) shows a range of approximately 4 to 24 percent. The incidence rate is higher in coroner's cases[15,61,70] and has also been traditionally thought to be higher in mental institutions[1,15,18,24,49,61,71–73] although Kavelman[74] found the incidence to be similar in psychotic and nonpsychotic patients in the same hospital. These higher rates are presumably the result of higher autopsy rates in coroner's cases and in institutionalized psychotic patients[73] and possibly the consequences of continued activity after clinically undetected myocardial infarction. Table II does not include the series of Jetter and White[48] from the Massachusetts Mental Institute in which a surprising 73 percent of mental patients who died of acute myocardial infarction were found to have had parietal rupture.

Most of the statistics quoted concerning incidence are derived from autopsy series, but two reports deserve special attention. One, by Sievers,[66] reviewed the cases of all patients with diagnosed myocardial infarction admitted to Malmo General Hospital, Sweden, during the 25 years from 1935 to 1959. This group had had 2,477 "attacks," of which 858 (34.6 percent) were fatal in the acute stage, defined as the first 4 weeks after clinical onset. Postmortem examinations, performed in 95 percent of these patients, revealed that 104 (12.5 percent) had cardiac rupture and hemopericardium. A second report, by Spiekerman et al.,[8] examined the population of Rochester, Minnesota between 1947 and 1959, a period when 1,326 persons died in and out of hospitals. Autopsies were performed on 691 patients who were 20 years or older. Eighty-seven died of acute myocardial infarction and 21 of these were found to have parietal rupture (24 percent). This figure is close to that reported by Crawford and Morris[70] in their epidemiologic study in London. Both the Swedish and Rochester studies are important since they have relatively few selection factors and probably represent more accurately than other investigations the true incidence in the population at large.

Risk Factors

Influence of age and sex: Age is a significant unfavorable risk factor not only for cardiac rupture but also for acute myocardial infarction.[75] Rupture is seldom seen before the 6th decade of life,[14,15,22,23,29,65,74,76] and the peak incidence occurs during and after the 7th decade.[1,13,15,19,21–23,25,26,29,31,34,51,52,77,78]

Although the overall rate of myocardial infarction is higher in men than women,[1,14] rupture is at least as frequent in women as in men.[14,15,23,26,28,31,34,47,71,77] As a result, it is generally believed that a woman with an acute infarct is more likely to have cardiac rupture than a man.[21,26,47]

Other cardiac disease: Many studies have stressed the importance of a clinical history of hypertension in the pathogenesis of cardiac rupture,[21–23,29,31,48] but Naeim et al.[14] found no such correlation. There is, however, a correlation between hypertension in the acute phase of myocardial infarction and rupture.[13–15,53] The occurrence of a greater incidence of hypertension but a smaller incidence of cardiac hypertrophy in cardiac rupture was noted by several investigators.[14,24,29,31]

Maher et al.[22] and others[24,49] found that patients who died of cardiac rupture were predominantly in a group with little or no cardiac failure. In the study of Wessler et al.,[15] 33 percent of the control subjects and only 5 percent of the patients with rupture had clinically evident congestive heart failure.

Anticoagulant agents: There have been reports[63,80] of an increase in cardiac rupture and hemopericardium in patients receiving anticoagulant therapy for acute myocardial infarction. However, Maher et al.[22] found no significant evidence to indicate that routine well-monitored anticoagulant therapy increases the risk of rupture in the immediate postinfarction period, and others[13,24,29,46] have confirmed their view.

Clinical Course and Diagnosis

Patients who die of a parietal rupture are characteristically older persons without a significant prior history of cardiac disease who are progressing to an uncomplicated recovery after their first infarction when cardiac rupture suddenly occurs. Persistent hypertension and the development of renewed or worsening chest pain without acute electrocardiographic changes may suggest impending or progressing cardiac rupture. The most common presentation is sudden unanticipated death although survival for up to 3 weeks after cardiac rupture has been reported.[95,96] The interval from the onset of clinically evident rupture to death is seldom measured

in more than minutes. Stupor, shock and terminal arrhythmias conclude the event.

Sudden chest pain, sinus or junctional bradycardia and hypotension occurring together during the early postinfarction period should suggest the possibility of cardiac rupture especially if signs of cardiac tamponade follow. Pallor, cyanosis, distended neck veins, a distant quiet heart and electromechanical dissociation are also consistent with rupture, but are not specific for it.

Diagnostic Investigation

Laboratory studies: In general, laboratory investigations have proved to be of little help in the diagnosis of cardiac rupture.[15]

Electrocardiography: Cardiac rupture is diagnosed terminally by sudden electromechanical dissociation often presenting with recurrent chest pain.[81,82] The most common underlying electrocardiographic pattern is that of recent transmural myocardial infarction;[83] other patterns are unusual.[26,84]

Although there is no single diagnostic electrocardiographic characteristic of impending cardiac rupture, the sudden appearance of tall T waves in the precordial leads just before rupture has been reported,[23,83,85] but this finding is also seen in acute hemopericardium secondary to rupture of the ascending aorta or sinus of Valsalva. It is possible that this electrocardiographic pattern results from a sudden increase in potassium concentration affecting myocardial repolarization when hemolysis of erythrocytes trapped in the pericardial sac occurs. Atrioventricular (A-V), junctional and idioventricular arrhythmias have been noted by many workers,[15,83,86,91] but probably often represent agonal events.

It has been suggested[37,82] that the observed bradycardias are mediated by vagal stimulation with the afferent limb originating in pericardial stretch receptors. The sequence of rhythm changes seems characteristic of impending or early cardiac rupture and may be of predictive value because it usually allows up to 10 minutes for urgent pericardiocentesis and management decisions.

More recently, Mir[87,88] described six patients with an acute myocardial infarction and an "M-complex" pattern in their electrocardiograms; all six died on their 1st day of coronary care unit management, and three died of cardiac rupture. The M-complex is a monophasic RS complex with an upright T wave and progressive S-T segment elevation. In the three cases of cardiac rupture, there was a rapid rise in the S-T elevation coincident with the onset of recurrent chest pain. Patients with recent acute myocardial infarction and sudden chest pain whose electrocardiograms record this pattern, particularly if associated with A-V block, A-V junctional arrhythmias or brief episodes of ventricular tachycardia, should be suspected of undergoing myocardial rupture.

The eventual diagnostic value of the various electrocardiographic signs of impending or progressive cardiac rupture remains to be seen, particularly in view of their frequently evanescent and sometimes vague characteristics. Because electrocardiographic recording is a simple and routine technique suitable for continuous monitoring, further careful studies of its use in diagnosing cardiac rupture are needed.

Echocardiography: Although in use for more than a decade, the role of echocardiography in diagnosing cardiac rupture has not been explored. Its effectiveness in the detection of pericardial effusions,[89,90] especially with the use of M mode scanning,[91,92] indicates that it may prove to be of use in assessing impending cardiac rupture. This would be especially true if cardiorrhexis were, at least in part, a chronic process preceded by the slow accumulation of blood in the pericardial sac presaging impending rupture. The gradual accumulation of fluid in the pericardial space may fail to produce significant clinical symptoms[93] and yet be detectable by echocardiography, which can detect effusions as small as 15 to 20 ml.[90]

Roentgenograms: Chest roentgenograms play an essential role in the diagnosis of ventricular aneurysm and pericardial effusion but lack specificity and are less useful in the early diagnosis of cardiac rupture.

Pericardiocentesis: This procedure can be lifesaving in acute cardiac rupture and tamponade but determination of when it should be performed remains a challenge.

Prognosis

As we have seen, cardiac rupture has proved to be almost universally fatal. Effective medical therapy is nonexistent. Surgical intervention in cases of cardiac rupture has remained, until recently, essentially speculative and the results have been poor.[17,81,94,95]

Therapy: Attempted Surgical Repair

Working on the assumption that acute electromechanical dissociation might be a specific and immediately recognizable sign of cardiac rupture, Cobbs et al.[81] instituted a 5 year prospective study during which they attempted the repair of three acute ventricular perforations secondary to myocardial infarction. There were two long-term survivors, and the feasibility of a combined medical and surgical approach to acute cardiac rupture was shown. One of the survivors sustained a right ventricular infarct in which massive pericardial hemorrhage appeared to be avoided by a relatively intact overlying epicardium. The second patient survived a 1 cm tear in the left ventricle. In both cases, pericardiocentesis confirmed the diagnosis of tamponade and greatly improved and stabilized the patient's condition preoperatively. In addition, the rate of hemorrhage appeared to slow after pericardiocentesis, possibly because of local clotting.

Close clinical observations, a high index of suspicion and aggressive surgical therapy have proved successful in five other reported instances of cardiac rupture.[17,94]

The long-term prognosis for patients surviving surgical repair of a ruptured ventricle may be excellent. For example, one patient survived 3 years and died of an unrelated cause[81]; another patient, 1 year after surgery, was participating in athletic activities, including cross-country skiing.[95]

TABLE III

Factors Indicating Increased Risk of Cardiac Rupture

1. Recurrent chest pain without electrocardiographic changes suggestive of another infarct or extension
2. Sustained hypertension after myocardial infarction
3. First myocardial infarction; no history of angina, or only recent history of angina
4. Less than 5 days since myocardial infarction
5. Patient 80 years or older

TABLE IV

Signs and Symptoms Suggesting Cardiac Rupture

A. Terminal signs
   1. Pericardial blood and tamponade
   2. Electromechanical dissociation
   3. Failure of closed chest resuscitation to produce peripheral pulses
B. Preterminal signs and symptoms
   1. Pericardial blood
   2. Recurrent severe chest pain without evidence of new infarct
   3. M-complex in electrocardiogram
   4. Suggestive echocardiographic changes

TABLE V

Suggested Therapy for Cardiac Rupture

Group	Clinical Impression	Possible Therapy: Hemodynamic and Angiographic Study	Possible Therapy: Diastolic Augmentation or Mechanical Assist	Possible Therapy: Operation
1	Obvious rupture	No	No	Yes
2	Suggestive with definite deterioration	If possible	If possible	Yes
3	Suggestive but condition stable	Randomize treatment		
		A. Yes B. Yes	A. No B. Yes	A. No B. Yes

Suggested Diagnostic and Therapeutic Approaches

The key to possible success in the treatment of cardiac rupture is the identification of those patients at greatest risk for cardiac rupture after myocardial infarction, combined with early diagnosis followed by prompt intervention. Table III lists some of the factors that indicate increased risk of rupture; Table IV outlines the events that might be observed during and before rupture.

There is now no organized approach to the management of cardiac rupture. The following outline describes a possible approach (Table V).

1. In patients exhibiting signs suggesting that rupture has already occurred (Table IVA), pericardiocentesis with proper needle positioning should be performed. If grossly hemorrhagic fluid is aspirated from the pericardium, pericardiocentesis should be continued, volume replacement begun and, if needed, open chest resuscitation instituted and the patient transferred without delay to the operating room. To stabilize the patient's condition between emergency thoracotomy and ventricular repair, a mechanical ventricular assistance device may be used while full cardiopulmonary bypass is being instituted.[96]

2. In patients in stable condition presenting with signs suggesting increased risk for cardiac rupture (Table III), serial echocardiograms should be performed daily to monitor pericardial fluid accumulation and to assess other variables. Constant electrocardiographic monitoring should be used, at least during the first 5 days. Any deterioration in the patient's condition (including recurrent chest pain without evidence of new infarction, M-complexes or new appearance of peaked T waves in the electrocardiogram, sudden development of right-sided heart failure, pulsus paradoxus or new pericardial friction rub) should indicate the need for rapid echocardiographic reassessment of pericardial fluid level. If the level is increased, aspiration should be performed and the presence of pericardial blood determined. If pericardiocentesis is grossly bloody and shows evidence of rapid reaccumulation then, if time permits, prompt intraaortic balloon insertion, cardiac catheterization and angiography should be performed before surgical exploration for repair of impending points of rupture and for revascularization.

3. In patients in stable condition and increased risk for cardiac rupture (Table III) but without obvious pericardial blood or pseudoaneurysm, therapy should be randomized. The medical group should be studied and treated with reduction of blood pressure. The surgical group should be studied, have intraaortic balloon insertion and emergency surgery to revascularize the myocardium where coronary arterial bypass grafting is technically feasible, with patching of sites of weakened myocardium. Randomizing such stable patients to medical or surgical groups will permit determination of which method of management is superior; it is likely that a multicenter trial would be needed to obtain sufficient numbers of such patients without obvious free rupture.

Conclusions

Despite 50 years of continuous interest in cardiac rupture and the important advances in cardiology and cardiovascular surgery, no major breakthrough in the diagnosis or treatment of this cardiovascular catastrophe has occurred. The true incidence in the population remains in doubt. The diagnosis is often missed or at best made only in the immediate premortem phase. Therapeutic attempts have not been of outstanding success up to the present time.

Recognition of this entity as a relatively common complication of acute myocardial infarction is needed. Detailed clinical and experimental studies on its pathogenesis still remain to be undertaken, and improved means of diagnosis must be developed. It is hoped that this review will stimulate further study of this important subject.

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Loeffler's Endocarditis Presenting as Mitral and Tricuspid Stenosis

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Loeffler's endocarditis characteristically produces cardiac dysfunction by the combined effects of endocardial fibrosis with restriction to diastolic inflow and intracavitary thrombosis with partial cavity obliteration. Although valve dysfunction may complicate this condition, it is rarely of primary hemodynamic significance. This report describes an unusual case in which mitral and tricuspid stenosis were the primary cardiac lesions. Because of the critical nature of the valve stenosis, surgical intervention was attempted despite evidence of left ventricular involvement. This case suggests than when significant valve dysfunction complicates Loeffler's endocarditis, surgical revision may be undertaken with at least temporary amelioration of the valve disorder and without apparent adverse effect on the underlying disease process.

In 1936 Loeffler[1] described two unusual patients who had marked persistent peripheral eosinophilia and a peculiar type of fibrosing endomyocarditis. Since then, similar cases with a primary apparently self-perpetuating increase in circulating eosinophils, diffuse organ involvement and frequent cardiac damage have been described.[2–5] The characteristic pathologic lesion in these patients is a dense endocardial fibrosis with superimposed thrombus.[1,5–7] The endocardial fibrosis prevents normal diastolic relaxation of the ventricular chamber, and the intracavitary thrombotic masses diminish ventricular cavity size. These lesions act in concert to diminish ventricular filling and decrease cardiac function, thereby producing a form of congestive heart failure similar to that seen with constrictive pericarditis. In addition to impairing the function of the heart as a pump, the endocardial fibrosis may extend to involve the papillary muscles and chordae tendineae, disrupting closure of the atrioventricular (A-V) valves and producing mitral or tricuspid insufficiency.[5,6] Because of the generally minor contribution of valve dysfunction to the overall syndrome,[1,6] the nature of the underlying pathologic process and the relatively guarded prognosis, no patient to date has undergone cardiac valve surgery.

This report describes an unusual patient with Loeffler's endocarditis whose presenting signs and symptoms were those of severe mitral stenosis. The presence of severe mitral and associated tricuspid stenosis was confirmed with echocardiography and cardiac catheterization. Because of the critical nature of the patient's valve disease and relatively well preserved ventricular function, mitral valve replacement was attempted. The unusual combination of mitral and tricuspid stenosis with Loeffler's endocarditis as well as the surgical procedure and postoperative course are described and discussed.

Case Report

The patient, a 35 year old white woman, presented with a 1 month history of increasing shortness of breath, orthopnea and ankle edema. Four years before admission a full-term twin pregnancy was complicated by ankle edema and mild shortness of breath. An increase in peripheral eosinophils was noted. No heart

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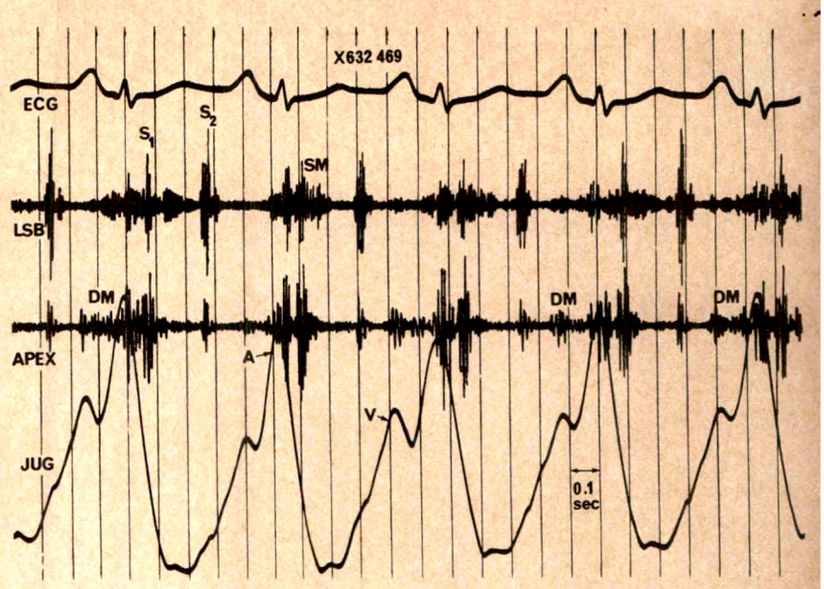


FIGURE 1. Electrocardiogram (ECG), phonocardiogram and jugular venous pulse tracing (JUG). The phonocardiogram recorded from the fourth left sternal border (LSB) and apex demonstrates a prominent first heart sound (S_1), diastolic rumbling murmur (DM) with presystolic accentuation and an even frequency systolic murmur (SM). The jugular pulse tracing illustrates the prominent *A* wave.

murmur was reported. After delivery, the patient was symptom-free until 2 months before this admission, when a dry nonproductive cough and easy fatigability developed. One month before admission she noted ankle edema and became short of breath with minor exertion. Two weeks before admission a physician noted a heart murmur consistent with mitral stenosis, and mild cardiomegaly, left atrial enlargement and bilateral localized lower pulmonary lobe infiltrates on chest X-ray examination. White blood cell count was 30,000/mm^3 with 87 percent eosinophils. Therapy with furosemide, digoxin and potassium chloride decreased her ankle edema. The shortness of breath and easy fatigability increased, and she was referred to this hospital for cardiac catheterization.

There was no past history of rheumatic fever, exposure to tuberculosis, hemoptysis, weight loss, fever or known heart murmurs. Two of her children had been treated for pinworms in the past year.

On admission she was dyspneic at rest. The temperature was 36.5° C, the pulse 100/min and respiratory rate 18/min. The blood pressure was 110/70 with an orthostatic drop to 80/10 mm Hg. No lymphadenopathy was noted. There was evidence of pulmonary consolidation in the left upper pulmonary lobe posteriorly. The heart was mildly enlarged. A right ventricular impulse was noted. A diastolic thrill was felt at the left sternal border, and a palpable second heart sound was noted in the pulmonary area; the first heart sound at the apex was increased in intensity. A grade 2/6 systolic murmur that increased with inspiration was heard at the lower left sternal border, and a grade 3/6 holosystolic blowing murmur heard at the left sternal border radiated to the axilla. There was a long diastolic rumble with marked presystolic accentuation at the apex. The jugular *A* wave was greatly increased (Fig. 1).

Hemoglobin was 13 g/100 ml and white blood cell count was 26,000 mm^3 with 58 percent eosinophils. Urinalysis revealed trace proteinuria and 5 red blood cells/high-power field. Serum electrolytes, creatinine, urea nitrogen and alkaline phosphatase levels were normal. Stool was negative for ova and parasites. Serum cortisol was 24 μg/100 ml. Serum immunoglobin (IG) determinations were IgG 2,600, IgA 520, IgM 300 (all abnormal) and IgD 2.1 mg/100 ml (normal). The antinuclear antibody and lupus erythematosus preparations were both normal on two occasions. Serum complement was normal. White blood cell alkaline phosphatase score was 28.

The bone marrow examination revealed a marked increase in orderly maturing eosinophils as well as increased monocytes, plasma cells and plasmacytoid lymphocytes. Mild enlargement of the liver and spleen were noted on technetium scan. Response to intermediate strength purified protein derivative (PPD) of tuberculin was nonreactive.

The electrocardiogram (Fig. 2) revealed normal sinus rhythm, prominent P waves in lead II with large biphasic P waves in lead V_1 suggesting biatrial enlargement and a

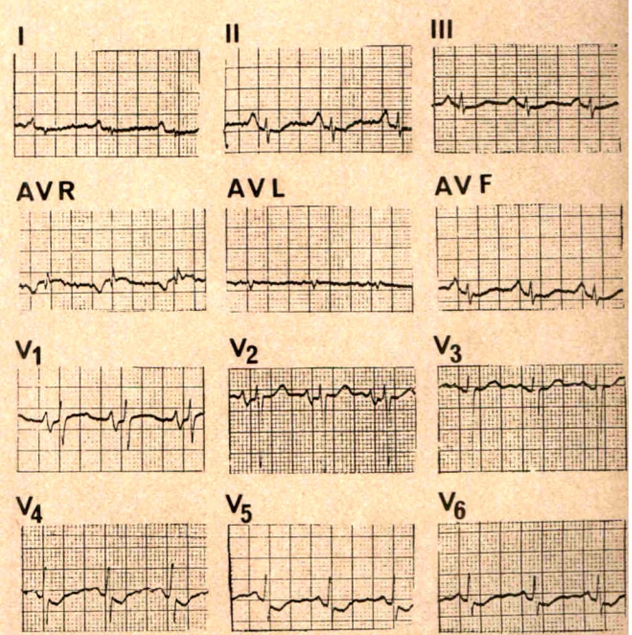


FIGURE 2. Electrocardiogram demonstrating biatrial and right ventricular enlargement.

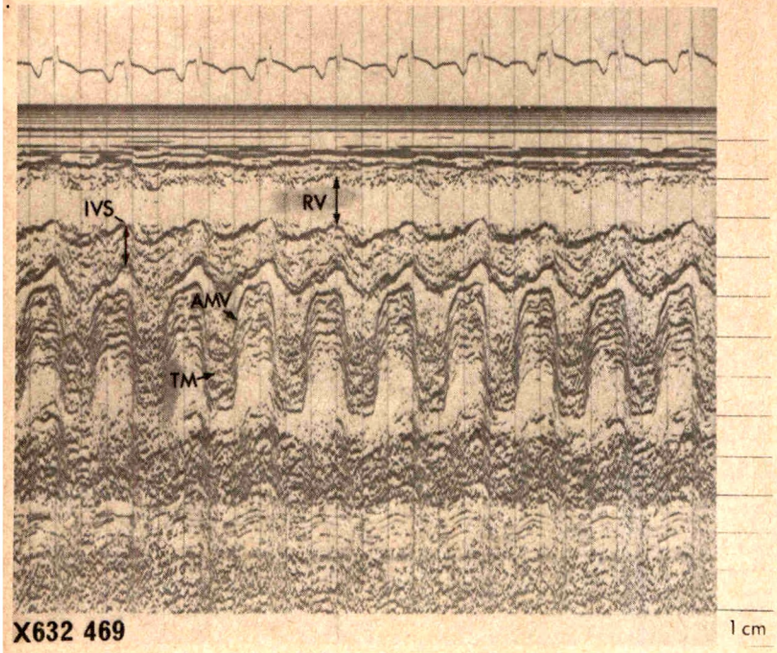


FIGURE 3. Echocardiographic recording from the area of the mitral valve. A dense echo-producing mass appears to be attached to the under surface of the anterior mitral leaflet (AMV) and moves in concert with the leaflet during both systole and diastole. There is also a reversal of the normal mitral E to F slope suggesting severe mitral stenosis with a persistent gradient across the valve throughout diastole. IVS = interventricular septum; RV = right ventricle; TM = thrombotic mass.

prominent R wave in lead V_1 suggesting right ventricular enlargement.

The echocardiogram (Fig. 3) revealed a large left atrium (4.0 cm) and thickening of the mitral valve echo with a decrease in E to F slope consistent with mitral stenosis. Opening mitral valve amplitude (D to E) was reduced to 11 mm. A mass of echoes attached to the posterior margin of the anterior leaflet moved in concert with the leaflet. The left ventricular cavity was small (3.2 cm). Septal motion and size were normal. The posterior left ventricular wall thickness was increased to 1.7 cm. The posterior endocardium was not well defined but appeared to blend in with a mass of echoes present along the endocardial surface of the posterior left ventricular wall. A scan from the aorta to the left ventricular cavity (Fig. 4) showed the anterior mitral leaflet echo to disappear into this area of granular-appearing echoes. The posterior mitral leaflet echo could not be clearly defined. There was a small posterior pericardial effusion. The tricuspid valve echo showed a decrease in E to F slope suggesting tricuspid stenosis (Fig. 5). The pulmonary valve echo showed loss of the *A* wave, flattening of the E to F slope and midsystolic closure of the valve indicating pulmonary hypertension.

Cross-sectional echocardiographic study revealed a mitral valve orifice area of 0.4 cm^2. The tricuspid valve echo showed restriction of anterior tricuspid leaflet motion consistent with tricuspid stenosis. The tricuspid valve orifice was not visual-

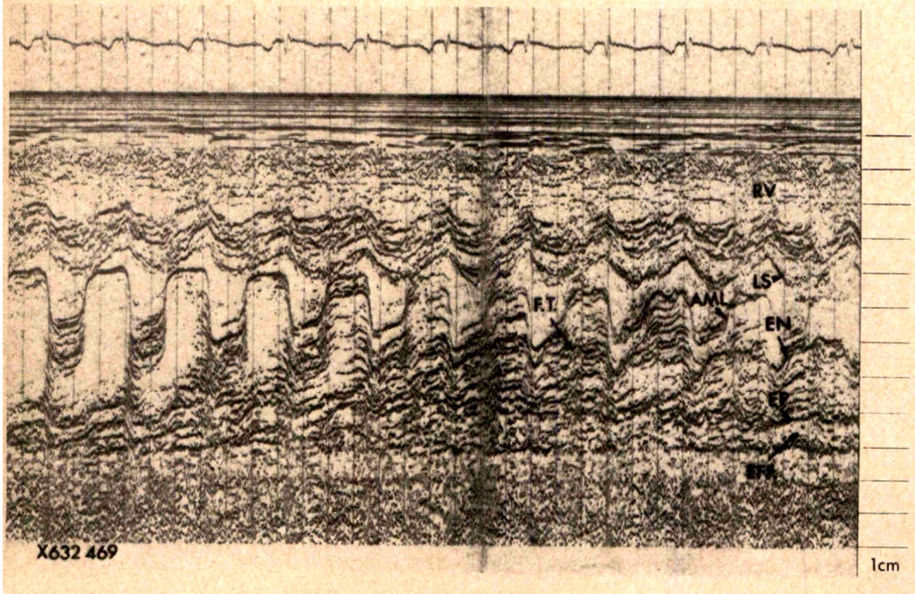


FIGURE 4. M mode echocardiographic scan from the left atrium and mitral valve into the cavity of the left ventricle. There is a dense buildup of granular-appearing echoes at the junction of the left atrium and left ventricle. The anterior mitral leaflet (AML) appears to blend into these granular echoes superior to the left ventricular wall. The posterior mitral leaflet is also buried within this mass of echoes. The posterior left ventricular wall is greatly thickened at the A-V junction. The echoes from the fibrinous thrombotic mass (F.T.) appear to be superimposed on the echoes from the left ventricular posterior wall. The left ventricular cavity is markedly diminished. Normal septal and posterior wall motion appear to be preserved. EFF = pericardial effusion; EP = epicardium; EN = endocardium; LS = left side of the interventricular septum; RV = right ventricle.

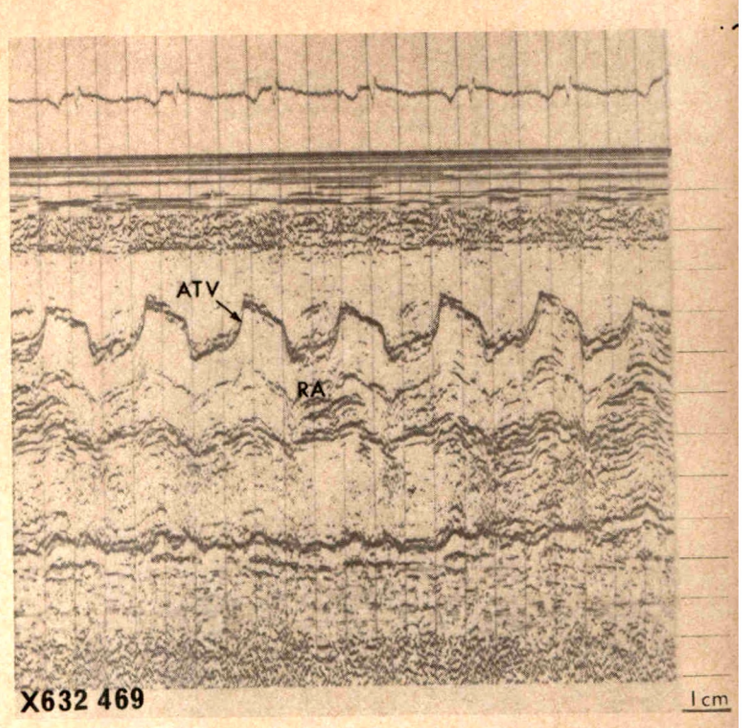


FIGURE 5. M mode recording from the tricuspid valve. A marked decrease in the tricuspid E to F slope suggests tricuspid stenosis. The right atrium (RA) is recorded behind the tricuspid valve. Beneath the right atrium are two linear echoes separated by a 2.6 cm echo-free space, probably representing the inferior vena cava. ATV = anterior leaflet of the tricuspid valve.

ized. The mass of echoes behind the anterior mitral leaflet was again noted.

The chest roentgenogram disclosed mild cardiomegaly with an enlarged left atrium (Fig. 6) and a prominent circular parenchymal infiltrate in the apical posterior segment of the left upper pulmonary lobe.

Cardiac catheterization revealed the following pressures (mm Hg): right atrial mean 4 with an *A* wave of 9 and a *V* wave of 5; pulmonary arterial 62/23 (mean 35); left atrial mean 31 with an *A* wave of 32 and *V* wave of 37; and left ventricular 90/6. The mitral valve gradient was 21.3 mm Hg and calculated mitral valve area 0.34 cm^2. The tricuspid valve gradient was 5.4 mm Hg with a calculated tricuspid valve area of 0.9 cm^2. The cardiac index was 1.3 liters/min per m^2. Dye dilution curves revealed mild mitral and tricuspid insufficiency. Cineangiograms revealed a normally contracting left ventricle with an irregular mass protruding beneath the posterior mitral leaflet.

Surgical findings: Because of the patient's incapacitating symptoms and the critical mitral valve area, mitral valve replacement was undertaken. A thickened mitral valve with a small opening was noted. A mass of fibrin-like material was adherent to both surfaces of the mitral valve. The chordae tendineae were infiltrated with the same material. The papillary muscles were fibrous in character. Both the anterior and posterior mitral valve leaflets were bound down by the mass of fibrinous material beneath the valve. The valve was removed and replaced with a no. 29 stent-mounted porcine heterograft. The tricuspid valve was inspected and found to be slightly thickened with fusion of the commissures between the septal and anterior leaflets. These commissures were opened, and the valve was left in place.

Microscopic sections of the endocardium and fragments of myocardium showed pronounced fibrous thickening of the endocardial layer. Diffuse infiltration with chronic inflammatory cells was noted. Very few eosinophils were noted outside the vascular lumens. The irregular mass underneath the posterior leaflet contained a large amount of relatively acellular homogeneous eosinophilic fibrin.

Postoperative course: The patient did well until approximately 3 weeks postoperatively, when atrial flutter and a large right pleural effusion were noted (Fig. 6C). A ventilation-perfusion lung scan at this time was compatible with pulmonary emboli. The patient continued to receive Coumadin® therapy, and conversion to sinus rhythm was successful. Complete blood count at this time showed 13,700/mm^3 white cells with 50 percent eosinophils.

During the subsequent 6 months the patient returned to her normal level of function with only minimal limitation. Her lungs remained clear, and there was no recurrence of the left upper pulmonary lobe infiltrate. A persistent grade 3/6 soft holosystolic murmur heard along the left sternal border was followed by an opening snap and a prominent diastolic rumble; both the systolic and diastolic murmurs increased markedly with inspiration. Serial echocardiograms (Fig. 7) demonstrated normal left ventricular function with a normally functioning mitral valve prosthesis. The pulmonary valve echogram returned to normal postoperatively. Complete blood counts demonstrated a persistent elevation of white cell count with more than 50 percent eosinophils.

Discussion

This report describes a young woman who presented with signs and symptoms of severe mitral and tricuspid stenosis and was later found to have a form of the hypereosinophilic syndrome or Loeffler's endocarditis. This case is unusual in that the primary cardiovascular manifestations were related to valve disease rather than to the restrictive myopathy normally occurring in these patients. Although the association of insufficiency of the mitral and tricuspid valves with Loeffler's endocarditis is well established, valve stenosis is less clearly described. Mitral valvulitis with insufficiency was noted

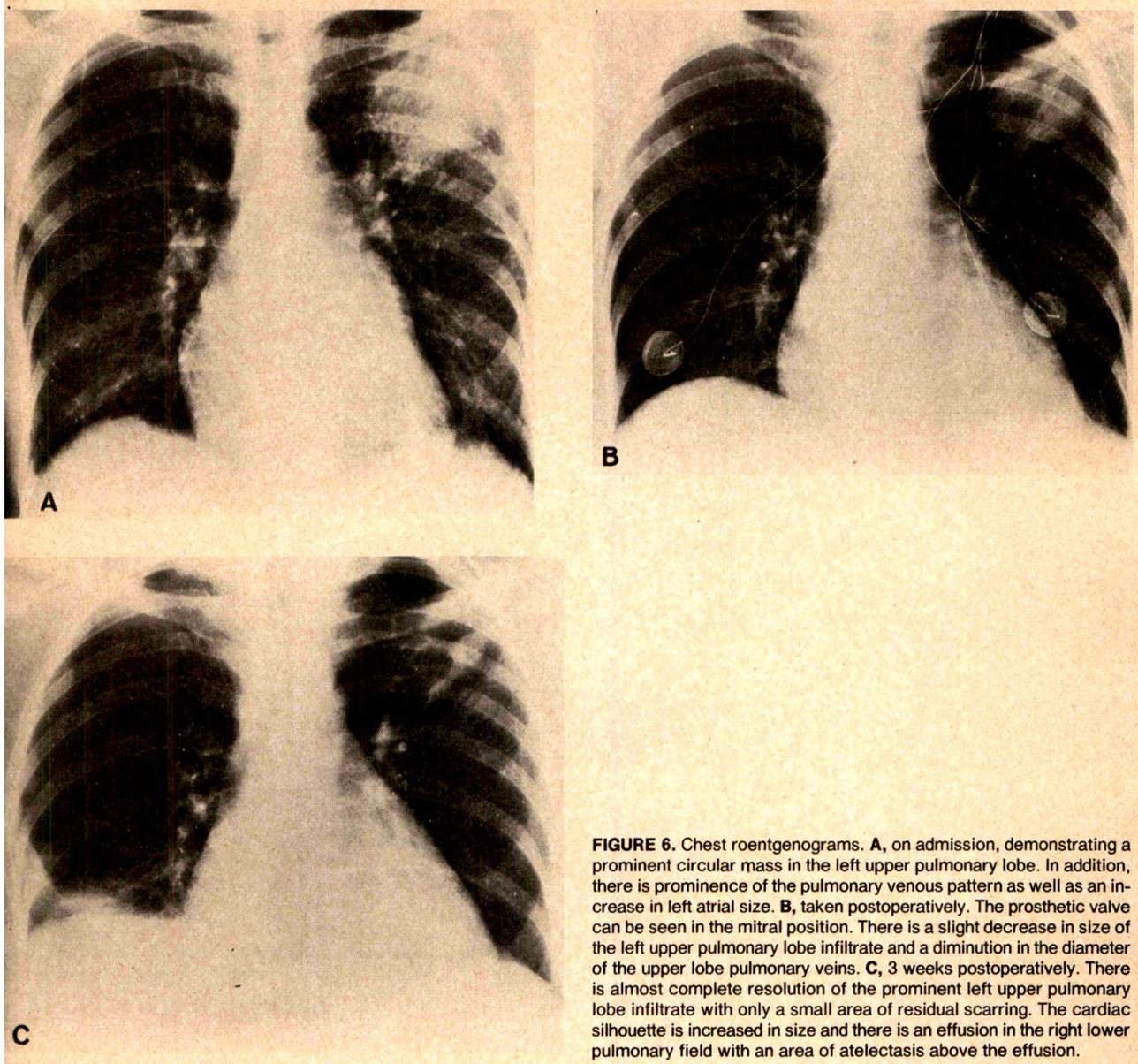


FIGURE 6. Chest roentgenograms. **A,** on admission, demonstrating a prominent circular mass in the left upper pulmonary lobe. In addition, there is prominence of the pulmonary venous pattern as well as an increase in left atrial size. **B,** taken postoperatively. The prosthetic valve can be seen in the mitral position. There is a slight decrease in size of the left upper pulmonary lobe infiltrate and a diminution in the diameter of the upper lobe pulmonary veins. **C,** 3 weeks postoperatively. There is almost complete resolution of the prominent left upper pulmonary lobe infiltrate with only a small area of residual scarring. The cardiac silhouette is increased in size and there is an effusion in the right lower pulmonary field with an area of atelectasis above the effusion.

n one of the original cases reported by Loeffler.[1] The ailure of the valve dysfunction to account for the pa- ient's symptoms and the prominent nature of the en- locardial lesions in these cases were emphasized. Brink nd Weber[6] in 1963 reviewed 40 cases of Loeffler's en- locarditis and in 20 cases they noted systolic murmurs ocalized to the apex that they attributed to mitral in- ufficiency. Chusid et al.[5] in a review of 57 cases noted alve damage, usually involving the mitral valve, in 18 ercent of patients subjected to autopsy. More than 50 ercent of the patients with cardiac symptoms had eart murmurs at some time during the course of their isease, and 50 percent of these murmurs were mitral n nature. Murmurs of valve insufficiency, 5 of mitral rigin, were present in 6 of these investigators' own 14 ases.

Postmortem studies indicate two main reasons for mitral regurgitation. First, there may be extensive nodular deposits or fibrous vegetations on one or both mitral leaflets.[8] Second, and more commonly, the posterior mitral valve leaflet because of its close anatomic relation to the posterior left ventricular wall becomes entrapped by the endocardial fibrous process preventing normal function.[9,10] These two parallel pathologic processes act singly or in concert to produce the relatively common valve insufficiency.

Pathologic basis for mitral and tricuspid stenosis: Stenosis of the mitral and tricuspid valves is far less frequent. Diastolic rumbling murmurs suggesting mitral stenosis were found in 3 of the 40 cases reviewed by Brink and Weber.[6] Mumme[11] described a patient with a prominent diastolic rumble whose postmortem ex-

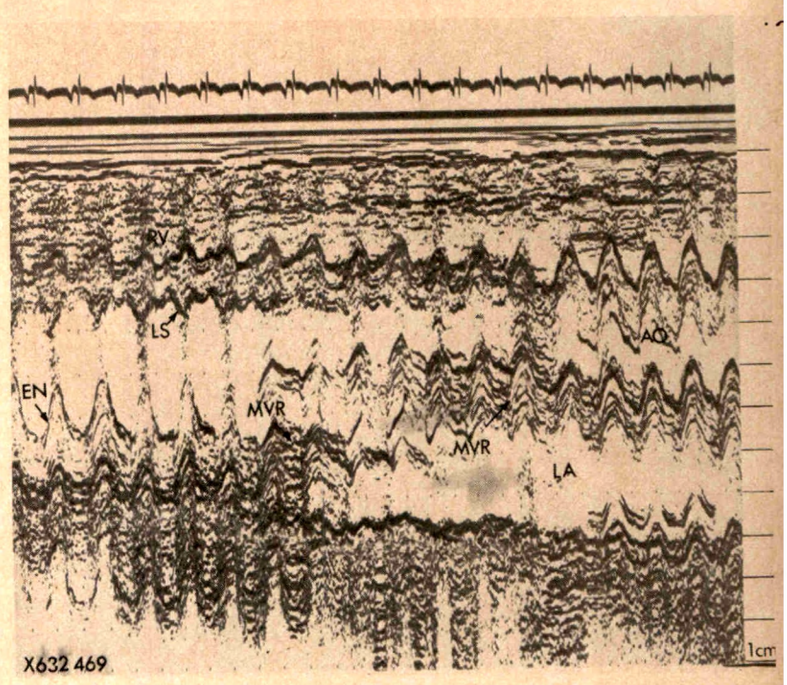


FIGURE 7. Postoperative M mode echocardiographic scan from the cavity of the left ventricle **(left),** to the aorta (AO) and left atrium (LA) **(right)**. The prosthetic mitral valve is visualized. The dense echoes from the valve ring are indicated (MVR). Left ventricular function distal to the area of the valve appears to be well preserved. There is no evidence of recurrence of the thrombotic material in the left atrial cavity. EN = posterior wall endocardium; LS = left septal surface; RV = right ventricle.

amination revealed the mitral and tricuspid valves and their respective chordae tendineae to be contracted and thickened. Dirty reddish wart-like vegetations were on the valve surfaces. The case described by Hoffman et al.,[12] from this institution, was remarkably similar to our present case. At autopsy the mitral valve orifice was narrowed, and there were large amounts of fairly firm brownish granular material attached to the atrial surface of the valve. The tricuspid valve orifice was also decreased in size and showed considerable fibrosis involving the valve, the chordae tendineae and the papillary muscles. Bell et al.[10] reported a case with severe tricuspid stenosis and mild tricuspid regurgitation. In our case the severe mitral and tricuspid stenosis prompted the patient's hospitalization. It was only later that the persistent hypereosinophilia, migratory pulmonary infiltrates, hepatosplenomegaly and associated cardiac dysfunction led to a diagnosis of Loeffler's endocarditis. It is conceivable that in this case, as well as in previously reported cases, the hypereosinophilic component may have been superimposed on preexisting rheumatic valve disease. In none of these cases, however, were heart murmurs described before the onset of the acute disorder, nor were Aschoff bodies found in the pathologic specimens in any case. In each case dense endocardial fibrosis with thickening of the papillary muscles, chordae and A-V valves was evident at autopsy.

Even if mild rheumatic valve stenosis were present as an underlying disorder, one would anticipate that the superimposition of the endomyocardial fibrotic process on already partially fused leaflets and chordae tendineae would lead to combined entrapment of both the anterior and posterior leaflets as opposed to only the posterior leaflet involvement normally seen. This more extensive entrapment or restriction of the already partially stenotic leaflets complicated by the deposition of fibrotic material on the atrial surface of the valve leaflets could combine to convert a mild or subclinical lesion into a severely stenotic one. Because no evidence for preceding rheumatic disease was present in any of these cases, it may be presumed that valve stenosis may occur as part of the primary clinical picture of the hypereosinophilic syndrome.

Surgical indications and results: Before we made the decision to operate on our patient, we considered two important questions. The first was whether the natural course of her underlying disease warranted extensive surgical intervention. The second was whether the surgical procedure itself might in some way aggravate the underlying disease. In many of the earlier studies, the diagnosis of Loeffler's endocarditis was made at postmortem examination. The time from the onset of symptoms to death in these patients was generally reported to be very short. Among the 40 cases reviewed by Brink and Weber,[6] 25 patients died within 1 year of the onset of symptoms. More recent studies indicate that the course of this disorder may be much more favorable. Of the 14 patients followed up by Chusid et al.,[5] the 12 who were alive at the time of the published report had a mean survival time of at least 5 years. Resnick and Myerson[13] reported on two patients with hypereosinophilic syndrome followed up for 11 and 17 years, respectively. Thus, although no satisfactory method of therapy has been discovered, and these patients must be followed up expectantly with only symptomatic treatment, the course of this disorder appears to be more favorable than originally suggested.

The effect of surgical intervention on the valve lesions in these patients is unknown. Although pericardiotomy has been performed in some patients given a mistaken

diagnosis of constrictive pericarditis,[14–16] ours appears to be the first case in which valve replacement was attempted. Bell et al.[10] recently described one case in which mitral anuloplasty was performed to correct a severely regurgitant mitral valve. Their patient has been followed up for 6 months and appears to be in improved condition. Our patient has also been followed up for 6 months postoperatively and to date has shown a marked alleviation of symptoms. As indicated by the postoperative echocardiogram (Fig. 9) there is good left ventricular function and apparent continued normal function of the porcine mitral valve. There has been no evidence of recurrence of the left atrial thrombus or deterioration of left ventricular function. There is persistence of tricuspid stenosis and insufficiency since the tricuspid valve was left in place and only a limited tricuspid valvulotomy performed.

Because the etiology of this disorder is unknown, we were concerned that extensive resection of cardiac tissue might expose fresh areas of myocardium to the circulating eosinophils and, in some way, exacerbate the disease process. It appears, however, that the underlying hypereosinophilia is less severe now than before operation. The pulmonary lesions have disappeared with only minimal residual scarring in the left upper lobe with no therapy other than the corticosteroids administered at the time of operation. The white blood cell and eosinophil counts, although elevated, have stabilized at a level lower than the preoperative level.

Echocardiographic findings: The echocardiogram in our case deserves some comment. In addition to establishing the diagnosis of mitral and tricuspid stenosis before catheterization and indicating the severity of the mitral lesion, the echocardiogram was very helpful in confirming the clinical suspicions concerning the underlying nature of the pathologic disorder. The marked increase in left ventricular posterior wall thickness and the tendency of the anterior mitral leaflet to disappear into the dense mass of echoes superior to the left ventricular posterior wall were atypical for rheumatic mitral stenosis and indicated some form of proliferative endocardial reaction involving both the anterior and posterior mitral leaflets. Second, the dense mass of echoes attached to the left atrial surface of the anterior mitral leaflet, which moved in concert with the leaflet and was present in only portions of the leaflet echo, was highly suggestive of some form of thrombotic or vegetative process attached to the posterior surface of the leaflet. This combination of findings could not be explained by typical mitral stenosis alone and appeared to be consistent with the eventual diagnosis of Loeffler's endocarditis.

The significant short-term improvement in this patient's clinical condition after surgical replacement of the mitral valve indicates the feasibility for surgical intervention in patients with Loeffler's endocarditis in whom valve disease represents the primary hemodynamic derangement.

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Displacement of the Heart by a Giant Mediastinal Cyst

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A giant mediastinal cyst caused marked cardiac displacement, factitious cardiomegaly and clinical and hemodynamic findings suggestive of constrictive pericarditis. The correct diagnosis was established with echocardiography and confirmed with angiography and surgery.

Echocardiography is of proved benefit in diagnosing a wide variety of structural cardiac anomalies. Its value in assessing cardiomegaly has been emphasized and it has also been successfully used to identify extracardiac anomalies simulating primary cardiac disease. This report exemplifies its utility in the latter setting.

Case Report

A 57 year old white woman was referred for evaluation of chest discomfort, dyspnea on exertion and ankle edema of 1 year's duration. There was no history of acute rheumatic fever, heart murmur, hypertension, myocardial infarction or chest trauma. Physical examination revealed a regular pulse of 80/min. The blood pressure was 130/80 mm Hg with 6 mm Hg of paradoxical pulse. The neck veins were distended 6 cm above the clavicles at 45°. The hepatojugular reflux was absent. The chest was clear to percussion and auscultation. A systolic impulse was present at the second right intercostal space and right sternal border. A pulsatile mass and a systolic thrill were noted in the right supraclavicular fossa. The heart sounds were normal but decreased in intensity from the left sternal border to the normal location of the cardiac apex. A loud systolic ejection murmur was audible over the entire precordium and was maximal over the pulsating mass in the right supraclavicular region. A smooth liver edge was palpable 3 cm below the right costal margin and was nonpulsatile. There was no ascites, but mild ankle edema was present. The peripheral pulses were all normal.

The electrocardiogram revealed normal sinus rhythm, low voltage in leads V_2 to V_6 and mild nonspecific T wave changes with little change in configuration from leads V_2 to V_6. The chest roentgenogram (Fig. 1A) revealed apparent cardiomegaly, a mass in the right upper lung field and a left pleural effusion. Initial diagnostic considerations included cardiomyopathy, aortic aneurysm and pericardial tamponade.

A standard M mode single transducer echocardiogram was obtained with the transducer located in the third and fourth left intercostal spaces, 1 cm from the left sternal border. Instead of the normal cardiac echoes, a large sharply demarcated echo-free space was identified. It measured 10 cm in the anteroposterior diameter and 8 cm in the lateral diameter (Fig. 2). With the transducer located over the pulsating mass in the second right interspace, a normal echocardiogram was recorded. It revealed normal chamber size, wall thickness and motion and normal aortic and mitral valve motion (Fig. 3). Pericardial effusion was not present. This study suggested that a huge cystic mass had displaced the heart to the right infraclavicular region.

Cardiac catheterization was performed to investigate the anatomy and hemodynamic consequences of this cystic mass. The study revealed equalization of diastolic intracardiac pressures. Right atrial mean pressure (mm Hg) was 14,

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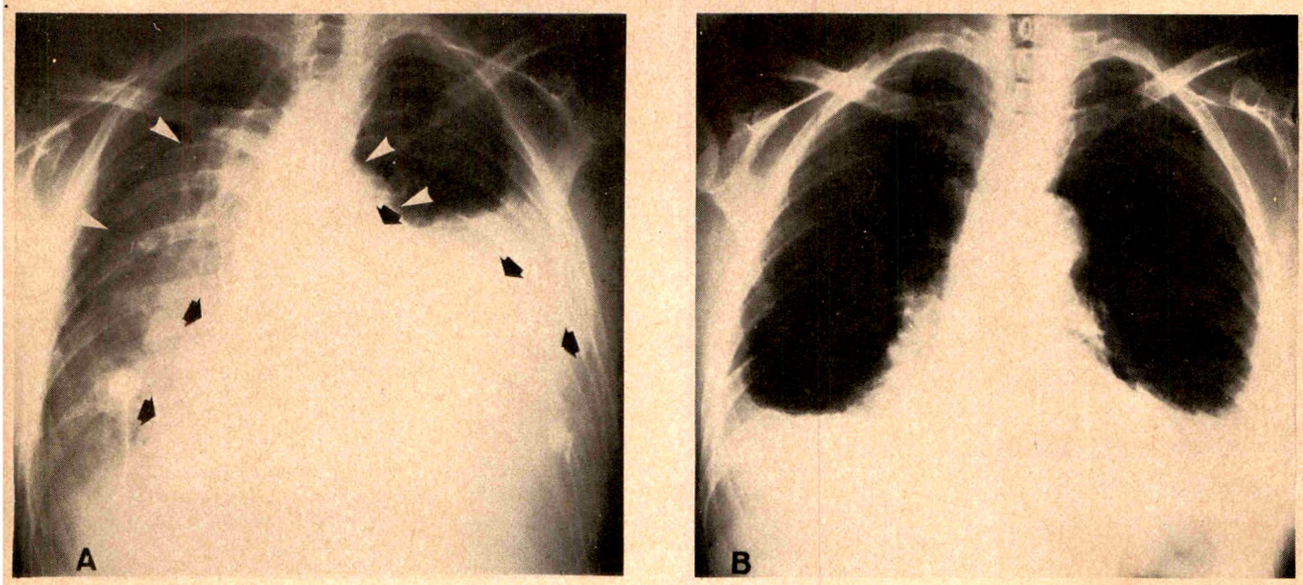


FIGURE 1. Chest roentgenograms. **A,** preoperative. The cyst margin is designated by the **black arrows**; the **white arrows** mark the displaced cardiac silhouette. **B,** postoperative.

right ventricular pressure 34/14, pulmonary arterial pressure 36/15, pulmonary capillary wedge pressure 14 and left ventricular pressure 130/14. The right atrial pressure had a rapid y descent, and the right ventricular diastolic curve conformed to the "dip and plateau" pattern of pericardial constriction. The displacement of the heart indicated in the echocardiogram was confirmed with left ventricular angiography. The left ventricle was deformed by a large nonopacified mass.

The patient underwent thoracotomy and a large anterior mediastinal mass was removed. The heart gradually returned to a more normal position (Fig. 1B). Examination of the mass (Fig. 4) revealed it to be a large benign fibrous cyst with organized hemorrhage on its inner surface. Grayish-red mucilaginous debris was found in the center of the cyst. No epithelial lining was present. The final pathologic diagnosis was organized hemorrhage that had undergone cavitation and fibrosis.

The patient did well postoperatively. Her symptoms were completely relieved and the murmur disappeared. Central venous pressure returned to normal immediately after operation. A repeat echocardiogram, with the transducer in the usual location, revealed normal cardiac structures and motion. The electrocardiogram also returned to normal. The patient was discharged on the 10th postoperative day.

Discussion

The differential diagnosis of mediastinal masses remains a difficult clinical problem. Mediastinal and pericardial masses may simulate many cardiac anom-

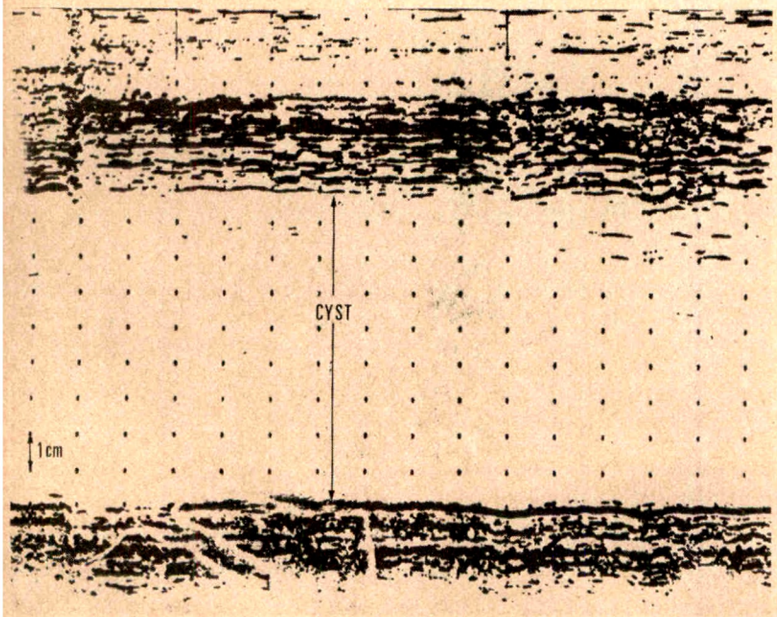


FIGURE 2. Echocardiogram obtained with the transducer placed in the fourth intercostal space at the left sternal border, showing a large echo-free space but no cardiac structures.

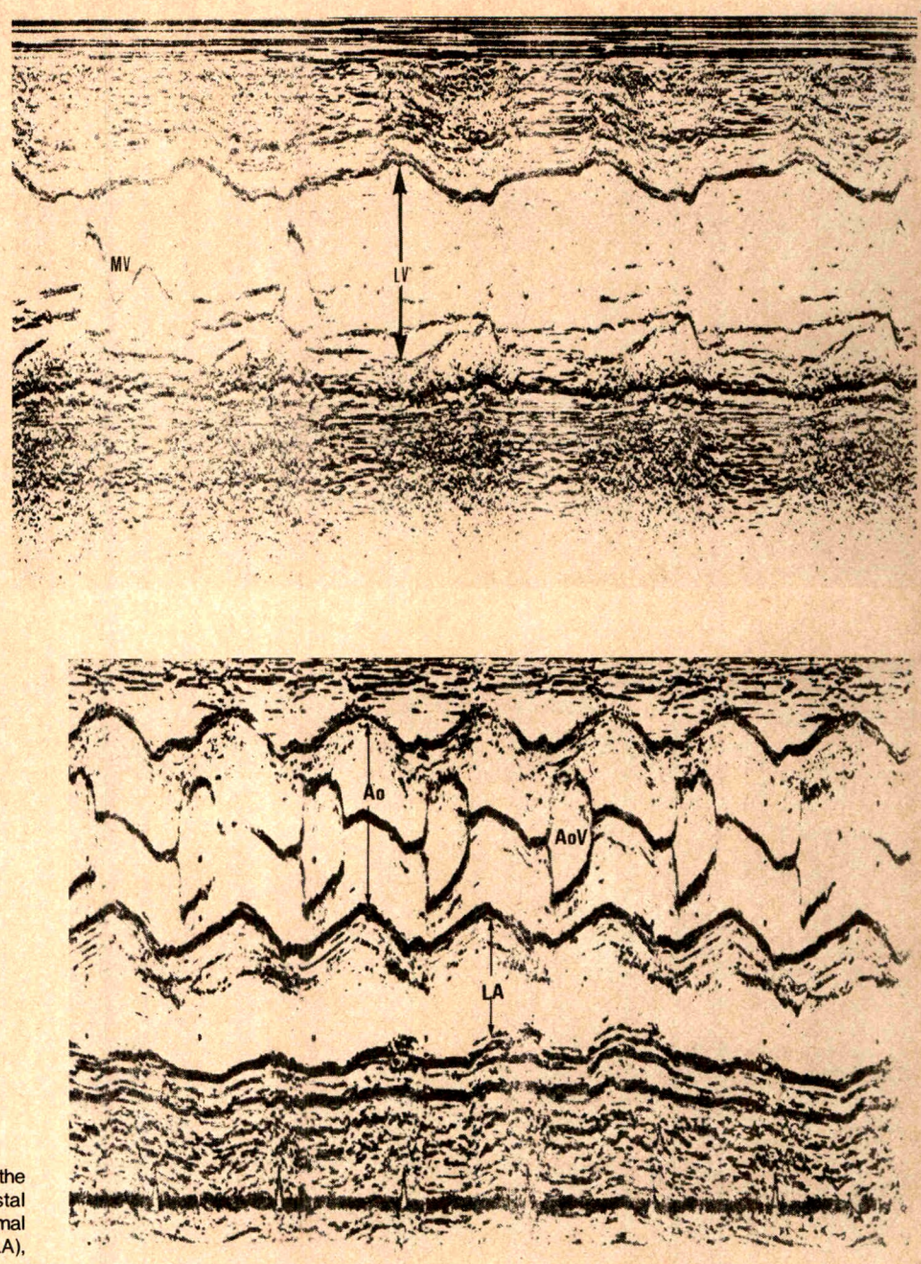


FIGURE 3. Echocardiograms obtained with the transducer placed in the second intercostal space, right midclavicular line showing normal aorta (Ao), aortic valve (AoV), left atrium (LA), left ventricle (LV) and mitral valve (MV).

alies and have been misinterpreted as representing cardiomegaly, aortic aneurysm[1] and pericardial effusion.[2] The origin of these masses can be lymphoreticular, neurogenic, teratomatous, pericardial, vascular, bronchogenic, enteric and mesenchymal.[3,4] A case has been reported of an esophageal duplication cyst that caused precordial and upper abdominal pain.[5] Cardiovascular hemodynamics may be significantly altered by mediastinal masses. Tumors located near the heart and great vessels can produce signs and symptoms that mimic tricuspid stenosis,[6] pulmonary stenosis[7] and constrictive pericarditis.[8] Invasive techniques are often required to provide accurate evaluation of these tumors. Several recent reports,[8–10] including one from this laboratory, have stressed the use of M and B mode echocardiography in the differential diagnosis of such tumors.

This case was remarkable because of the displacement of the heart into the right upper quadrant of the chest. The correct diagnosis was inapparent from the chest roentgenogram because the cyst could not easily be differentiated from a normally located but enlarged heart. Echocardiography demonstrated the actual location of the heart and revealed the cystic nature of the tumor and provided accurate data on its internal dimensions. Our case also demonstrates that mediastinal masses may produce hemodynamic alterations. Increased diastolic intracardiac pressures, identical to the pattern seen in constrictive pericarditis, have been seen in a case of cystic thymoma.[8] In our case, the heart

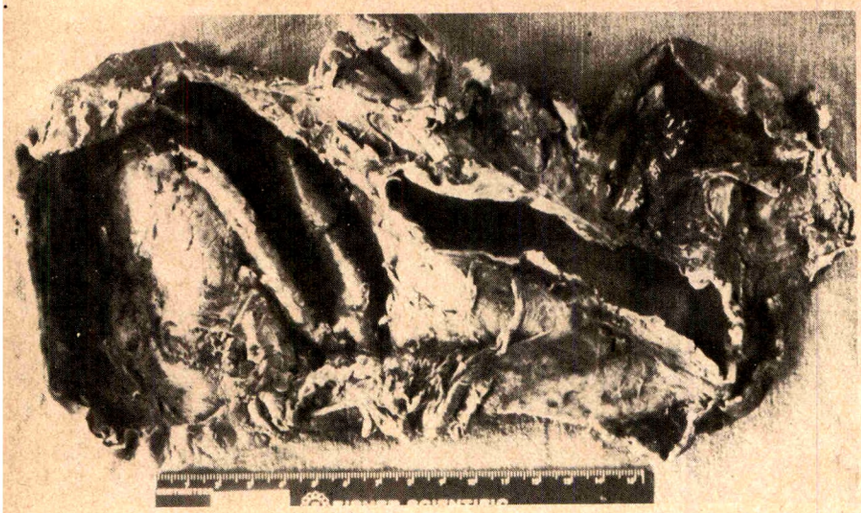


FIGURE 4. The opened cyst after removal from the thorax.

was pinioned between the cyst and the chest wall. Although the right heart pressures were only moderately elevated, the diastolic equalization of right and left heart pressures suggests an element of constriction. The patient's murmur may have been due to "kinking" of the great vessels by abnormal cardiac position or pressure on the right or left ventricular outflow tracts. The dyspnea may be explained by the increased right atrial pressure and the large intrathoracic mass that decreased vital capacity.

The origin of this lesion is obscure. It is unclear how long the patient had this mass in her chest; no history of trauma, previous surgery or bleeding diathesis was elicited.

Our case illustrates the valuable diagnostic role of echocardiography in clarifying the actual location and normalcy of the displaced heart and the cystic nature of the mass that shifted it.

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Echocardiographic Study of Malfunction of the Bjork-Shiley Prosthetic Heart Valve in the Mitral Position

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This report presents an echocardiographic study of four cases of malfunction of the Bjork-Shiley prosthetic heart valve in the mitral position. The malfunction was proved in all patients by cardiac catheterization, observation at cardiac surgery or findings at postmortem examination. Two distinctive motion patterns of the malfunctioning valves were detected in the echocardiogram. One was a rounded and slowed pattern of opening and closure that correlated with the presence of abnormal clotting on the prosthesis (two patients). The other was an unusual "hump" during the opening phase that correlated with significant perivalve leak (two patients). These patterns along with other observations appear to be valuable in recognizing mitral valve Bjork-Shiley prosthetic malfunction with echocardiography.

The echocardiographic appearance of the normally functioning Bjork-Shiley prosthetic heart valve has been described in vivo and in vitro.[1,2] In addition, echocardiographic manifestations of Bjork-Shiley valve malfunction in the aortic position have been described.[3,4] However, there have been no reports of echocardiographic studies dealing with Bjork-Shiley valve malfunction in the mitral valve position. This report presents four such cases together with echocardiographic findings that appear to be of considerable diagnostic value.

Materials and Methods

Echocardiograms were obtained with a Smith-Kline Ultrasonoscope equipped with a 2.25 megahertz transducer 1.6 cm in diameter. Permanent recordings were performed utilizing a Honeywell recorder set at a paper speed of 50 mm/sec. The echocardiograms were obtained with the patient in the supine position with the head elevated about 30°. The transducer was positioned at the third and fourth left intercostal spaces 2 to 4 cm to the left of the left sternal border and directed toward the level of the mitral valve; the orientation of the beam was adjusted to obtain maximal disc excursion in each case. The remainder of the echocardiographic examination was performed in accordance with previously described standard techniques.[5]

Case Reports

Patient 1: This 42 year old woman with rheumatic heart disease had a Bjork-Shiley prosthesis placed in the mitral valve area in March 1975. She did well until April 1976 when increasing orthopnea and dyspnea on exertion developed. No metallic "click" of valve action was present on physical examination. The chest X-ray film revealed pulmonary edema. Cardiac catheterization revealed pulmonary hypertension with a mean pulmonary capillary wedge pressure of 33 mm Hg and a simultaneous left ventricular end-diastolic pressure of 7 mm Hg. Left ventricular cineangiography revealed insignificant mitral insufficiency. An echocardiogram (Fig. 1A) showed decreased amplitude of excursion of the opening of the disc with a "rounded" upstroke and downstroke. At operation, numerous clots causing marked impairment of disc motion were found in the left atrium and on the prosthetic valve. The clots were removed and free disc motion was reestablished. The postoperative echocardiogram (Fig. 1B) showed the anticipated normal upstroke and downstroke pattern of this prosthesis.

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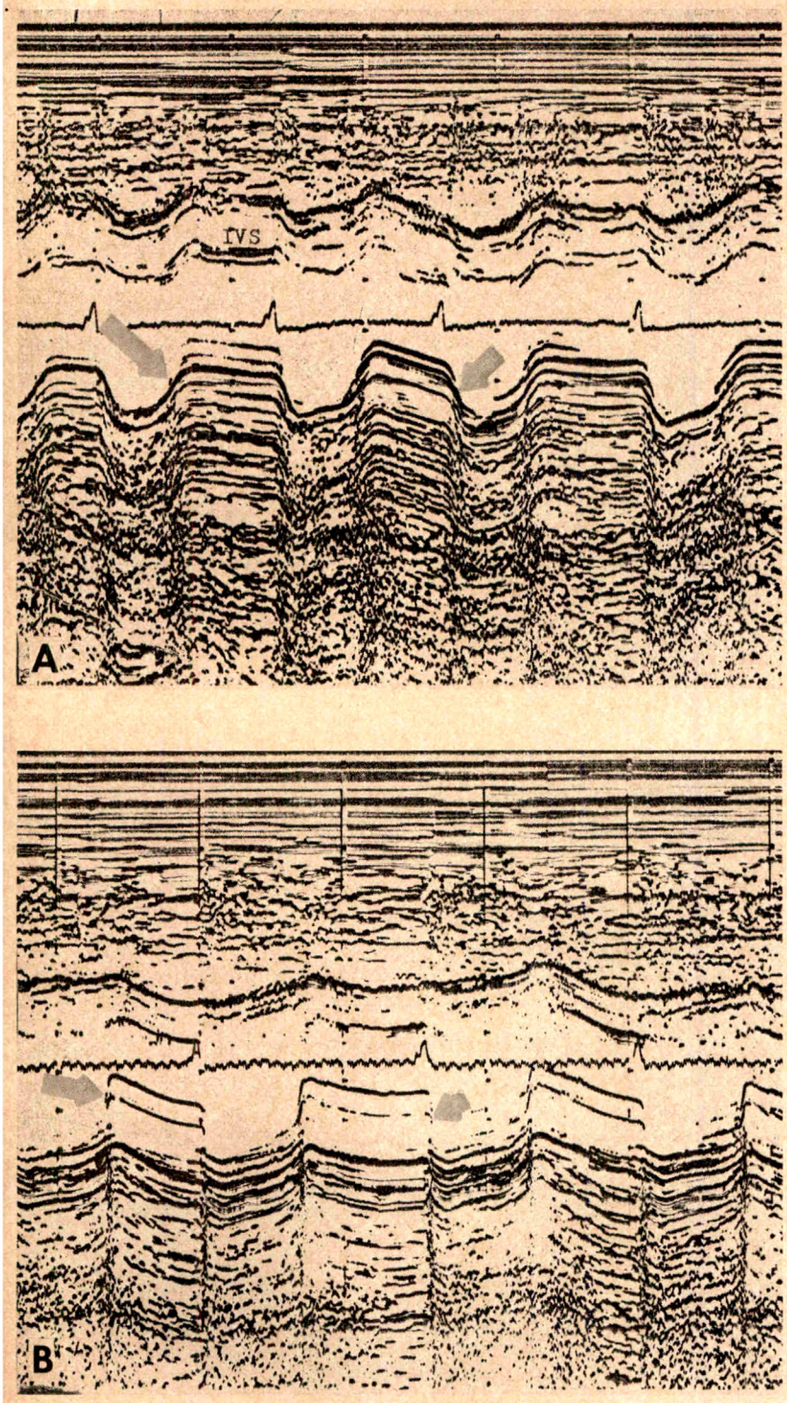


FIGURE 1. Case 1. **A,** preoperative. Visualization of the Bjork-Shiley mitral valve prosthesis showing a slowing and "rounded" opening upstroke **(larger arrow)** with an opening rate of 70 mm/sec as well as a slowed and "rounded" closing downstroke **(smaller arrow)** with a closing rate of 110 mm/sec. Also note diminished amplitude of excursion (8 mm) of the valve and the flat nonvariable slope during diastole. IVS = interventricular septum. **B,** postoperative echocardiogram showing normalization of the opening rate **(larger arrow)** to 240 mm/sec and normalization of the closing rate **(smaller arrow)** to 370 mm/sec. A variable diastolic slope can be seen in different cycles. The amplitude of excursion is now 10 mm.

Patient 2: This 39 year old man with marked mitral insufficiency underwent Bjork-Shiley prosthetic replacement of the mitral valve on December 6, 1975. His condition improved during the ensuing 3 weeks, but subsequently began to deteriorate progressively. An echocardiogram (Fig. 2A) showed very active septal motion in the direction of the left ventricular posterior wall during systole. The normal opening and closing speeds of the disc were preserved, but a unique "hump" was present in early diastole (Fig. 2B). In the operating room, a loose suture was noted that produced a leaking area about 10 mm in diameter. The prosthetic valve was replaced. Postoperatively the echocardiogram (Fig. 2C) showed diminished septal motion and disappearance of the "hump" previously seen on disc motion.

Patient 3: This 37 year old woman with rheumatic heart disease underwent Bjork-Shiley prosthetic replacement of the mitral valve in October 1973. In July 1975 severe dyspnea developed. The echocardiogram (Fig. 3) showed a slowed "rounded" opening and closing abnormality of the disc. The

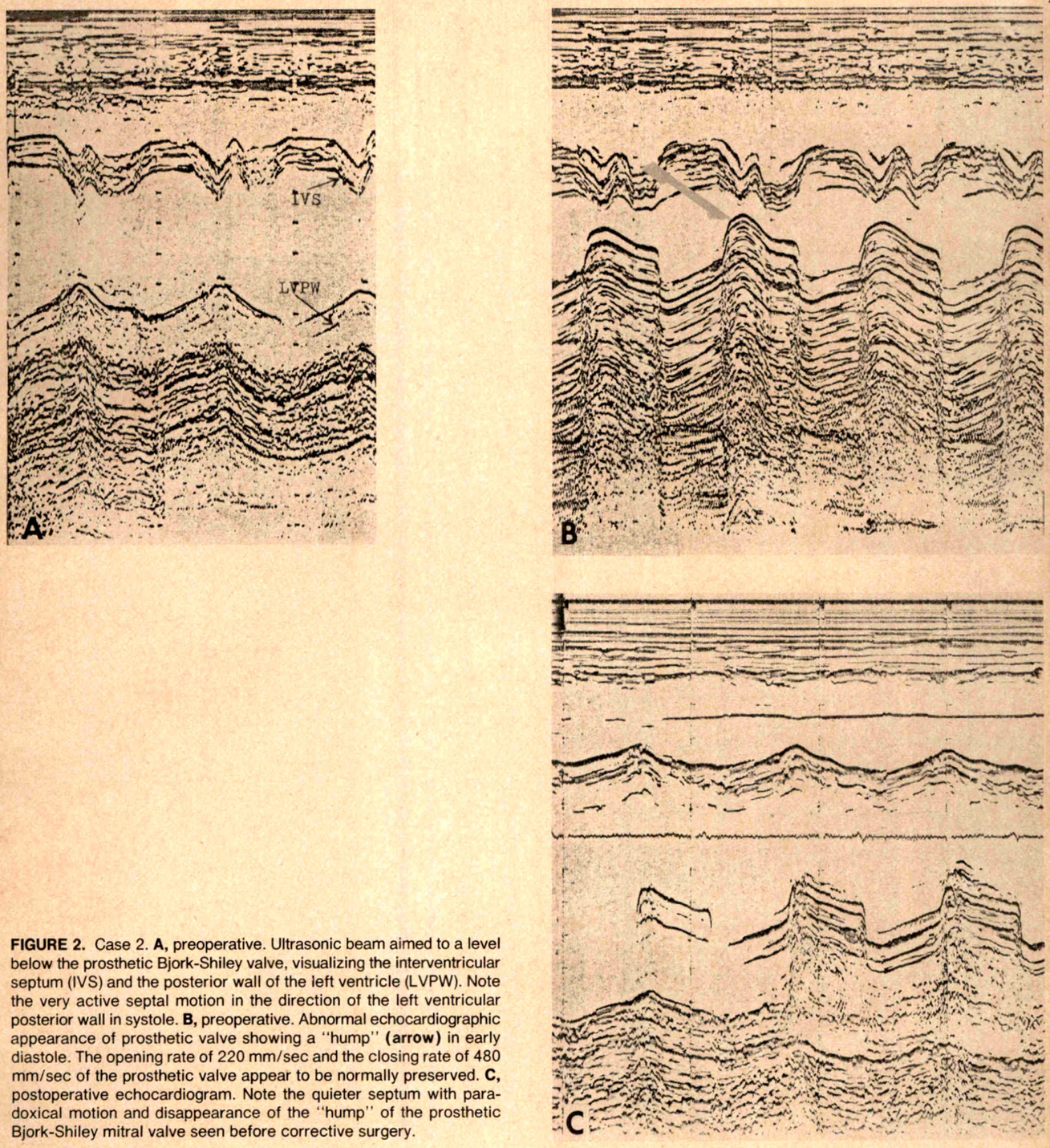


FIGURE 2. Case 2. **A,** preoperative. Ultrasonic beam aimed to a level below the prosthetic Bjork-Shiley valve, visualizing the interventricular septum (IVS) and the posterior wall of the left ventricle (LVPW). Note the very active septal motion in the direction of the left ventricular posterior wall in systole. **B,** preoperative. Abnormal echocardiographic appearance of prosthetic valve showing a "hump" **(arrow)** in early diastole. The opening rate of 220 mm/sec and the closing rate of 480 mm/sec of the prosthetic valve appear to be normally preserved. **C,** postoperative echocardiogram. Note the quieter septum with paradoxical motion and disappearance of the "hump" of the prosthetic Bjork-Shiley mitral valve seen before corrective surgery.

patient died suddenly before surgery could be undertaken. At postmortem examination extensive clotting was found in the prosthetic valve with marked impairment of disc motion.

Patient 4: This 39 year old woman with rheumatic heart disease underwent Bjork-Shiley valve implantation in the mitral valve area on December 2, 1975. One week postoperatively dyspnea, cyanosis and hypotension developed. An echocardiogram (Fig. 4A) showed a unique "hump" in early diastole. Left ventricular cineangiography confirmed a large perivalve leak. Corrective surgery was performed and the postoperative echocardiogram (Fig. 4B) showed normal motion pattern of the prosthetic valve.

Discussion

Prior echocardiographic evaluation of the Starr-Edwards prosthetic valve in the mitral position has

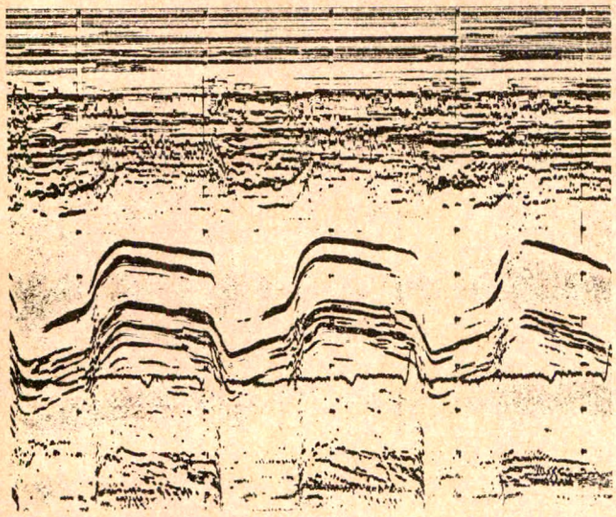
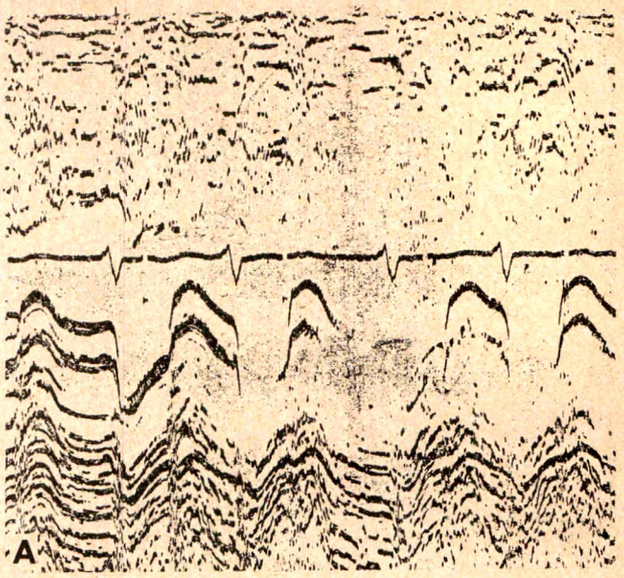


FIGURE 3. Case 3. Echocardiogram of a patient with autopsy-proved Bjork-Shiley mitral valve malfunction secondary to clotting (compare with Fig. 1A).



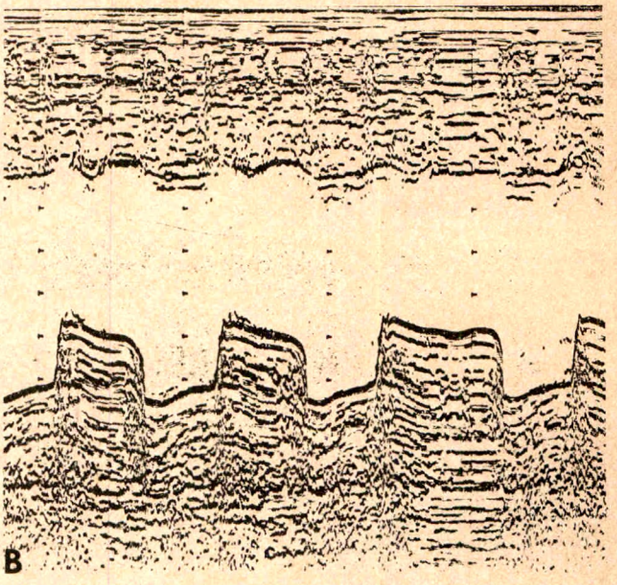


FIGURE 4. Case 4. **A,** preoperative. Visualization of the prosthetic mitral valve showing a "hump" in early diastole (compare with Fig. 2B). **B,** echocardiographic appearance of the prosthetic Bjork-Shiley valve after corrective surgery.

shown that the motion patterns are the result of both ring and ball motion.[6,7] Echocardiographic assessment of the Bjork-Shiley prosthetic valve in the mitral valve position is more complicated because of the spatial asymmetry of the tilting disc with this valve. However, our study has revealed two distinctive patterns of Bjork-Shiley mitral valve malfunction.

Malfunction due to valve clotting: Patients 1 and 3 had valve malfunction secondary to clotting. In our laboratory we expect normally functioning Bjork-Shiley valves in the mitral position to have opening rates exceeding 180 mm/sec and closing rates exceeding 300 mm/sec. In Patients 1 and 3 diminished amplitude of excursion and delayed opening and closing of the disc with a "rounded" upstroke and downstroke, as well as a flat pattern (without variable slope) during diastole, were noted. These features are probably due to impaired disc motion secondary to "stickiness" and "cushioned" oscillations caused by the clot formation. Their disappearance after corrective surgery with removal of the clots supports this contention.

Perivalve leaks: Patients 2 and 4 had Bjork-Shiley valve malfunction secondary to perivalve leaks. The distinctive feature of their echocardiogram was the disc "hump" in early diastole. Whether this pattern resulted primarily from abnormal ring motion or from abnormal intrinsic motion of the oscillating disc was not determined. Increased flow across the mitral valve prosthesis (at the time of rapid ventricular filling) because of the associated mitral insufficiency could be a factor.

In patients undergoing Starr-Edwards prosthetic replacement of the mitral valve "abnormal" or paradoxical septal motion in the echocardiogram is the expected favorable postoperative finding. The finding of "normal" septal motion in this setting has been correlated with perivalve leaks and valve malfunction.[8] Similar changes in septal motion were noted in analogous patients in this study with Bjork-Shiley valve malfunction.

At present, postoperative echocardiographic study with emphasis on septal and tilting disc motion appears to be of great assistance in the noninyasive establishment of Bjork-Shiley prosthetic valve malfunction in the mitral position. The importance of postoperative baseline echocardiographic tracings cannot be overemphasized.

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Hypoplasia of the Left Ventricle: Rare Cause of Postoperative Mortality in Tetralogy of Fallot

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Severe left ventricular hypoplasia in tetralogy of Fallot is a rare complication. A case history of a 3 year old child who died after attempted repair of tetralogy is presented. Left ventricular end-diastolic volume was 26 ml/m^2 (only 45 percent of predicted normal) after repair with normal filling pressure and no evidence of tamponade. Clinical examination, chest X-ray film, electrocardiogram and qualitative assessment of a preoperative left ventriculogram were not useful in assessing this degree of left ventricular hypoplasia; quantitative determination of left ventricular volumes is required for this purpose. When left ventricular end-diastolic volume is less than 55 percent of predicted normal, a shunt procedure may be indicated as an initial procedure with subsequent repair 1 to 2 years later, after left ventricular enlargement.

It has been suggested that death from low cardiac output in the immediate postoperative period after correction of tetralogy of Fallot can be due to a small left ventricle.[1] The incidence rate of this complication is low, and most reports of inadequate left ventricular size associated with postoperative mortality have been subjective. This report describes a patient who died after repair of tetralogy with a low cardiac output and a left ventricle that was less than 50 percent of normal size. Although severe hypoplasia of the left ventricle is rare in tetralogy,[1-6] this case demonstrates that this complicating feature cannot be diagnosed without quantitative volume measurements.

Case Report

A 3 year old boy presented to Vanderbilt University Hospital for total correction of tetralogy of Fallot. Cyanosis was first noted at age 6 weeks. Cardiac catheterization at the University of Tennessee Memorial Hospital demonstrated typical tetralogy of Fallot. Right and left ventricular pressures were 140/5 and 140/8 mm Hg, respectively. There was a 100 mm Hg gradient across the right ventricular outflow tract and pulmonary valve. The patient also had a patent ductus arteriosus. Systemic oxygen saturation was 94 percent. By age 3 years, there were marked cyanosis, dyspnea on exertion and frequent squatting.

Repeat catheterization revealed equal right and left ventricular pressures. The pulmonary artery could not be entered. On right ventricular angiography (Fig. 1), severe infundibular pulmonary stenosis, a large right to left ventricular shunt and a main pulmonary artery more than one third of the ascending aorta in diameter were demonstrated. A left ventricular angiocardiogram (Fig. 2) revealed a normally shaped left ventricle, a small left to right ventricular shunt and normal coronary arterial distribution.

On admission to this hospital, the patient was severely cyanotic and had marked clubbing. His respiratory rate was 28/min. He had a harsh grade 3/6 systolic murmur, maximal at the third left intercostal space, and a single second heart sound. The hematocrit was 71 percent. The chest roentgenogram demonstrated a typical boot-shaped heart and right aortic arch (Fig. 3). The electrocardiogram exhibited a frontal plane axis of ±125°, right atrial enlargement and right ventricular hypertrophy (Fig. 4); lead V_4R showed a qR pattern with a q wave of 1 mm and an R wave of 25 mm (10 mm = 1.0 mv). Left heart forces appeared to be normal.

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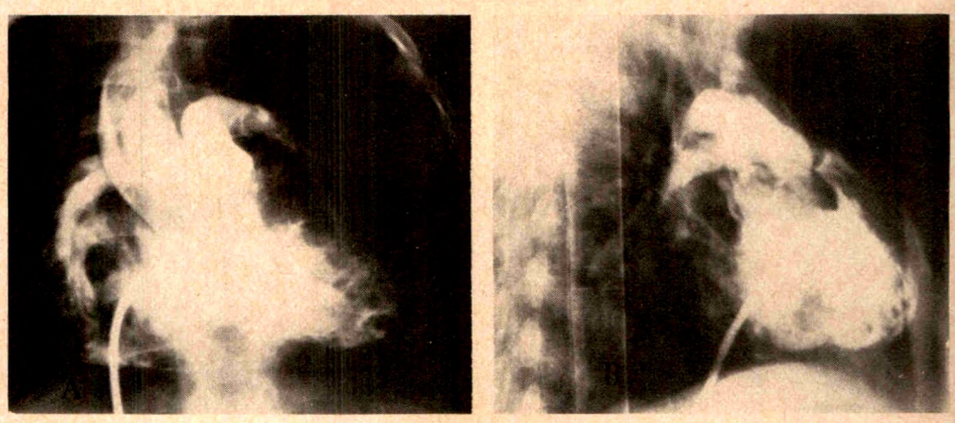


FIGURE 1. Right ventricular angiocardiograms showing severe infundibular pulmonary stenosis and large right to left shunt at the ventricular level.



FIGURE 2. Left ventricular angiograms showing a left ventricle of normal contour. There is a small left to right shunt at the ventricular level. The coronary distribution appears grossly normal. The aortic arch is on the right.

The patient underwent total repair[7] of tetralogy of Fallot on February 25, 1976. At operation the main pulmonary artery and left ventricle were noted to be small. A large amount of fibromuscular obstructive tissue in the right ventricle was resected, and the ventricular septal defect was closed with a double velour Dacron® patch. The pulmonary valve was tricuspid and the pulmonary valve anulus was small. The anulus was incised and a pericardial patch placed across it. Total bypass time was 70 minutes at 28 °C. The patient was weaned from cardiopulmonary bypass without difficulty and initially appeared to have adequate cardiac output. His initial blood gases were partial pressure of oxygen 142, partial pressure of carbon dioxide 43 and pH 7.38 during intake of 50 percent inspired oxygen. He was reexplored for mediastinal bleeding 4 1/2 hours after the reparative procedure. After this operation, he required a constant infusion of isoproterenol and epinephrine to maintain a blood pressure of 70/30 mm Hg, a pulse rate of 190/min and a urinary output of 0.5 cc/kg per hour.

Because of persistent mild hypoxemia and low cardiac output, cardiac catheterization was performed approximately 26 hours after the initial operation. Oxygen saturation was 93 percent in the aorta compared with 59 and 61 percent, respectively, in the right ventricle and main pulmonary artery during an intake of 50 percent inspired oxygen. There was no systolic gradient across the right ventricular outflow tract. A

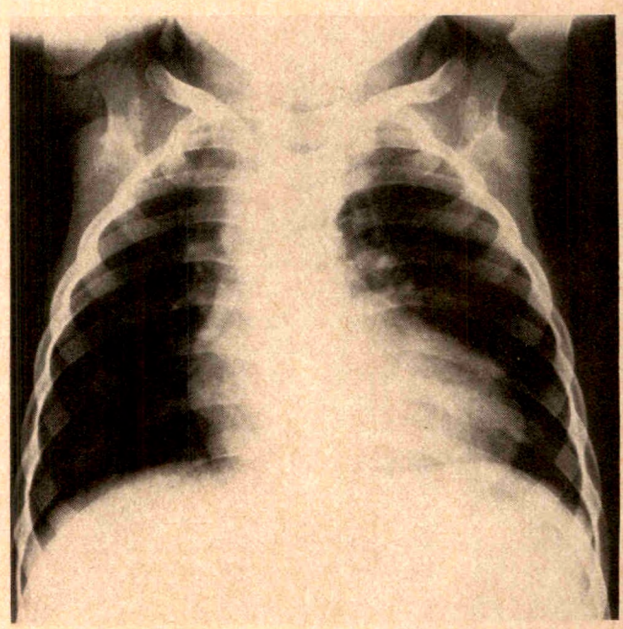


FIGURE 3. Chest X-ray film showing slight cardiac enlargement in the transverse diameter with the apex of the heart tilted up and a concave main pulmonary segment.

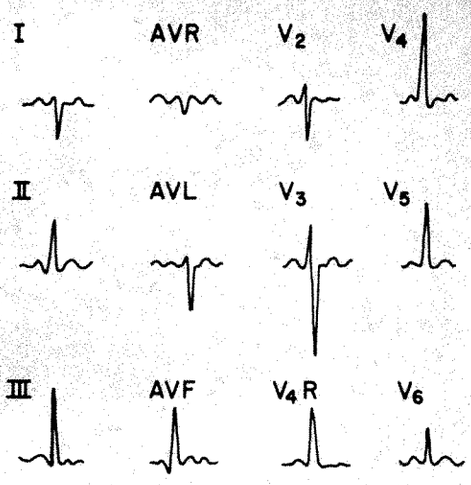


FIGURE 4. Electrocardiogram revealing a frontal axis of ±125°, right ventricular hypertrophy and normal left heart forces.

pulmonary arteriogram disclosed mild pulmonary insufficiency. With a heart rate of 150/min, left ventricular end-diastolic volume calculated from the levogram phase[8] was 26 ml/m^2 (only 45 percent of predicted normal); left ventricular ejection fraction was 0.52 (82 percent of normal) and systolic output 2.047 liters/min per m^2 (47 percent of normal). After return to the intensive care unit the patient had a cardiac arrest from which he could not be resuscitated.

Postmortem examination revealed the ventricular septal defect patch to be intact. There was no evidence of residual right ventricular outflow tract obstruction or cardiac tamponade. The tricuspid, mitral and aortic valves appeared normal. Left ventricular chamber size appeared small. The coronary arterial distribution was normal.

Discussion

This patient had a documented small left ventricle that was inadequate to sustain normal cardiac output after total correction of tetralogy of Fallot, despite adequate filling pressure and the administration of isoproterenol and epinephrine. Postoperative cardiac catheterization and autopsy examination failed to demonstrate a residual ventricular defect. Although a pericardial patch was placed across the right ventricular outflow tract and pulmonary valve anulus, there was no residual outflow tract obstruction. The chest X-ray film, electrocardiogram and qualitative assessment of the preoperative left ventriculogram were not useful in predicting the left ventricular hypoplasia.

Jarmakani et al.[4] described one patient who underwent total correction of tetralogy of Fallot whose left ventricular end-diastolic volume was less than 60 percent of normal. This infant died in the immediate postoperative period with left ventricular failure and pulmonary edema. Kirklin and Karp[1] reported on a 7 year old patient who died after correction of tetralogy of Fallot and whose left ventricular volume was considered too small to maintain an adequate cardiac output. In this child a good cardiac output was sustained only by raising the left atrial pressures to a level that precipitated pulmonary edema. Woodson et al.[9] described infants with tetralogy of Fallot who died of low cardiac output in the absence of hypovolemia or tamponade in the early postoperative period, but they did not present volume data.

Left ventricular volume in tetralogy of Fallot and surgical implications: In a series of 81 patients with repaired tetralogy of Fallot reported on from our institution,[7] 5 died postoperatively. Only two of these children died in the immediate postoperative period with low cardiac output; in these two cases the left ventricular end-diastolic volume was 89 and 113 percent of normal, respectively.

Preoperative left heart volume data are available for 21 children from this institution who have undergone primary repair of tetralogy in the last 4 years. Left ventricular end-diastolic volume was less than 75 percent of normal in six of these patients (29 percent), ranging from 64 to 74 percent of normal. Only one of these patients died after repair, a 15 month old with a left ventricular end-diastolic volume of 74 percent of normal who died with gram-negative septicemia 48 hours after operation. Two additional patients with respective values of 65 and 68 percent of normal did well with an initial shunt procedure and subsequent repair 2 to 3 years later after left ventricular enlargement had occurred. These data suggest that mild left ventricular hypoplasia with values for end-diastolic volume as low as 65 percent of normal is not a contraindication to primary repair. When left ventricular end-diastolic volume is 55 percent or less of the normal value, we believe that a shunt procedure is indicated as a first procedure. Values between 55 and 65 percent may be indications for an initial shunt procedure, but there are not enough data to be certain about this point.

Several factors other than a small left ventricle can contribute to low cardiac output after correction of tetralogy of Fallot. The right ventricle also is usually mildly decreased in size in cyanotic patients with tetralogy.[5,6] In addition, a right ventriculotomy as well as resection of hypertrophied crista supraventricularis can contribute to decreased right ventricular function. A patch across the right ventricular outflow tract and pulmonary valve permits a variable degree of pulmonary valve regurgitation and produces an acute volume load on a hypertrophied right ventricle. Pulmonary regurgitation usually is tolerated well if there is no pulmonary hypertension. If there is any residual right ventricular outflow obstruction, right ventricular function can be impaired further.

Clinical implications: Despite these problems, the overall mortality rate for repair of tetralogy is now approximately 5 percent in several recent series.[7,10–14] In an attempt to reduce this rate further, quantitative cineangiocardiography can play a role in selecting out the rare patient with severe left ventricular hypoplasia (end-diastolic volume 55 percent or less of the normal value) for an initial shunt procedure. The patient described herein illustrates that clinical examination, chest X-ray film, electrocardiogram and qualitative assessment of a left ventricular angiogram cannot select these patients preoperatively and that quantitation of left ventricular volumes is required for this determination.

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Chest Pain and Bilateral Atrioventricular Valve Prolapse With Normal Coronary Arteries in Isolated Corrected Transposition of the Great Vessels

Clinical, Angiographic and Metabolic Features

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A man evaluated for disabling chest pain was found to have isolated anatomically corrected transposition of the great vessels. Angiography demonstrated right and left atrioventricular (A-V) valve prolapse and normal coronary arteries. Atrial pacing produced chest pain, ischemic electrocardiographic changes, abnormal myocardial lactate metabolism and marked elevation of the left ventricular end-diastolic pressure; all of these changes returned to normal on termination of pacing. The association of corrected transposition and bilateral A-V valve prolapse and the possible causes of myocardial ischemia in this patient are discussed.

Isolated corrected transposition of the great vessels is an uncommon problem and is rarely associated with chest pain.[1] Chest pain with normal coronary arteriograms has frequently been noted in patients with and without atrioventricular (A-V) valve prolapse, but an association with corrected transposition has not been described. We describe herein a patient with isolated corrected transposition, disabling chest pain and bilateral A-V valve prolapse and discuss the clinical, angiographic and metabolic features encountered.

Case History

The patient, a 49 year old man, was admitted to the Cooper Green Hospital for evaluation of chest pain. He was well until September 1972, when he was admitted to a local hospital with chest pain and was told of possible myocardial infarction. In February 1973 he began to have recurrent episodes of anterior chest pain with radiation into the neck; the episodes occurred with exertion and anxiety and were relieved with rest. He was reevaluated, told he had angina pectoris and given nitroglycerin. During the subsequent year, he continued to have recurrent chest pain several times weekly in a stable pattern. Over the next 2 years his chest pain gradually increased in frequency. One week before admission he had an episode of severe retrosternal pain associated with shortness of breath, nausea and diaphoresis lasting 20 minutes and relieved after three nitroglycerin tablets. Over the next few days he had recurrent episodes of similar pain, including several episodes of nocturnal chest pain, and he required 10 to 12 nitroglycerin tablets daily. A history of a heart murmur since childhood was reported but was not associated with any symptoms or physical limitation. There was no history of rheumatic fever or family history of heart disease.

Physical examination on admission revealed a well developed thin man with a blood pressure of 100/70 mm Hg and regular pulse of 70/min. A slightly high arched palate was noted. Jugular venous pressure was 6 cm with normal *A* and *V* waves. Carotid pulsations were normal. The chest was clear on auscultation. Cardiac examination revealed the point of maximal impulse in the fifth intercostal space medial to the mid clavicular line, and somewhat diffuse and sus-

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tained. The heart sounds were normal with physiologic splitting of the second sound. An intermittent midsystolic click was present along the left sternal border and a grade 2/6 mid systolic murmur was present along the left sternal border with poor radiation. An electrocardiogram showed a normal P-R interval, increased anterior precordial forces and the pattern of left ventricular hypertrophy with strain. The chest roentgenogram showed a narrow vascular pedicle and an abnormal convexity of the left heart border (Fig. 1). Admission laboratory studies were normal, and an echocardiogram was interpreted as normal. The patient was observed in a coronary care unit. He continued to have recurrent episodes of severe chest pain, but no evidence of myocardial infarction was detected. Treatment with isosorbide dinitrate and propranolol resulted in some alleviation of his symptoms.

Cardiac catheterization was performed on June 14, 1976 with use of a transfemoral approach. Right and left heart pressures and cardiac index were normal. No intracardiac shunts or valve gradients were detected. Angiocardiography demonstrated corrected transposition of the great vessels. There was situs solitus with discordant A-V connections. The ventricles were inverted and in a side by side relation with the ventricular septum oriented in the sagittal plane. The systemic ventricle arose on the left and was a morphologic right ventricle with heavy trabeculations and a prominent infundibulum. The left A-V valve was tricuspid and showed a prolapse of the septal leaflet into the left atrium without valve regurgitation (Fig. 2). Contrast injection of the venous ventricle demonstrated a morphologic left ventricle with continuity of the pulmonary valve and the anterior leaflet of the inverted mitral valve. There was moderate prolapse of the bicuspid right A-V valve, and mild regurgitation into a slightly enlarged right atrium was seen (Fig. 3). The coronary arteries arose from the aorta in a mirror image of normal, as is usual with inverted ventricles,[2] and no obstructive lesions were demonstrated.

Myocardial metabolic studies: After cardiac catheterization the patient continued to have recurrent episodes of chest pain despite administration of maximal tolerable doses of nitrates and propranolol. On June 29, 1976, a myocardial metabolic study with atrial pacing was performed. The experimental protocol used in this study has been reported by Hill et al.[3] Pacing was performed using a Gorlin bipolar electrode catheter positioned in the coronary sinus. Left ventricular pressures were recorded before pacing, sequentially after 3 minutes at each paced rate, upon termination of pacing and at 30 second intervals for 5 minutes during the recovery period after pacing. Arterial and coronary sinus pH, partial

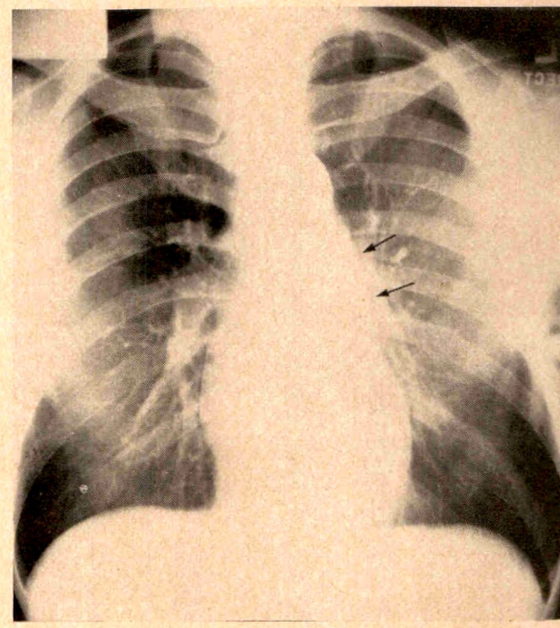


FIGURE 1. Chest roentgenogram showing situs solitus of the viscera and atria, normal pulmonary vascularity and the smooth curvilinear border (**arrows**) that represents the ascending aorta in *L*-position.

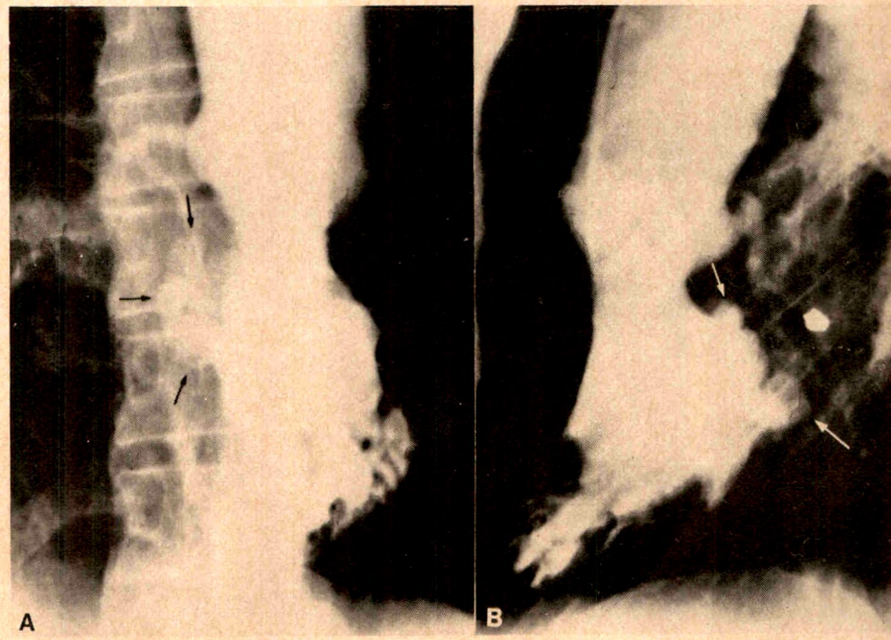


FIGURE 2. Systemic ventricular angiogram in anteroposterior (**A**) and lateral (**B**) views. The inverted right ventricle is of normal size and the aorta arises from it through a very well developed conus. Prolapse of the inverted tricuspid valve (**arrows**) is demonstrated. The ascending aorta forms the left upper mediastinal border.

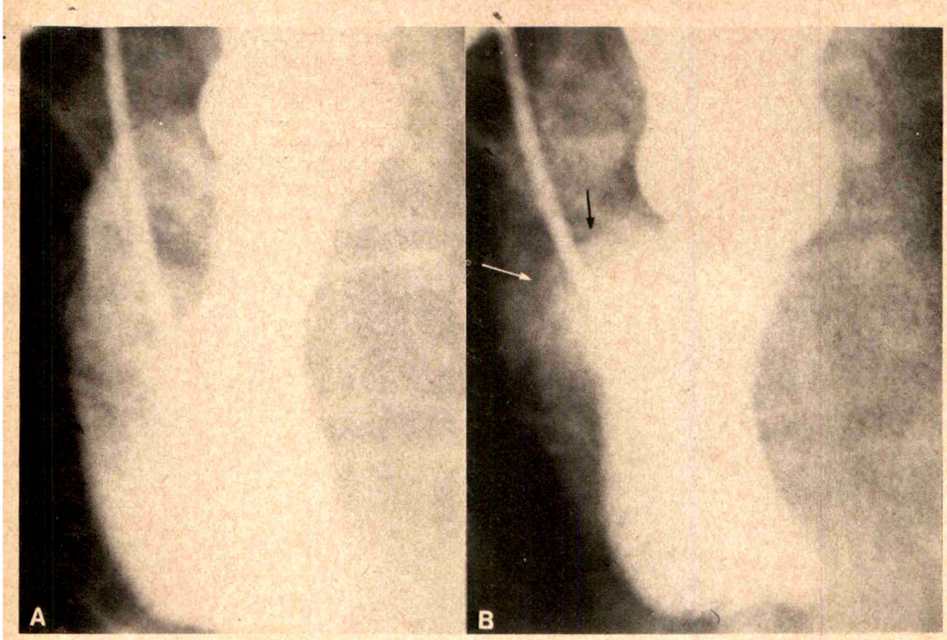


FIGURE 3. Venous ventricular cineangiogram in diastole (**A**) and systole (**B**) shows the inverted left ventricle to be of normal size and the pulmonary artery arising from the left ventricle in pulmonary-mitral continuity. Prolapse of the posterior mitral leaflet (**arrows**) is seen as a scalloped protrusion.

TABLE I

Myocardial Pacing Study

	Control HR (beats/min)	Pacing HR (beats/min)						Recovery HR (beats/min)					
	65	93	100	115	125	136	146	71	71	70	75	75	75
LVP (mm Hg)	107/10	112/3	118/3	113/0	117/6	115/10	117/32	127/18	118/16	117/15	130/15	120/13	118/8
S-T depression (mv)	5.0	3.5	4.0	5.0	6.5	7.5	8.0	6.5	6.0	6.0	5.0	5.0	4.0
Chest pain	. . .	. . .	. . .	. . .	. . .	+	+++	+++	+++	++	+	+	−

HR = heart rate; LVP = left ventricular pressure; − = absent; + = mild; ++ = moderate; +++ = severe.

pressures of oxygen and carbon dioxide, blood lactate, glucose and free fatty acid concentrations were obtained before pacing, at an intermediate (136/min) and a peak (146/min) pacing rate and after 5 minutes of recovery. Samples were analyzed as previously described.[3]

Atrial pacing was initiated at a heart rate of 93/min and increased at 3 minute intervals to rates of 100, 115, 125, 136 and 146/min (Table I). Left ventricular end-diastolic pressure decreased at the early paced rates of 93, 100 and 115/min and returned to the control level with further increases in heart rate (125 and 136/min). S-T segment depression present before pacing was diminished at the paced rates of 93 and 100/min, returned to control level at a paced rate of 115/min and increased to 1.5 mm below the control level at a paced rate of 125 beats/min. At a paced rate of 136/min, the patient experienced heavy retrosternal chest pain, and the electrocardiogram showed a 2.5 mm S-T depression below the control S-T level. Control lactate, glucose and free fatty acid extraction values were normal and were not significantly changed at the onset of chest pain. Further pacing at 146/min was associated with progressively severe retrosternal chest pain, and atrial pacing was terminated at this heart rate. Left ventricular end-diastolic pressure increased to 32 mm Hg, the electrocardiogram showed 3 mm S-T segment depression below the control level, and myocardial lactate extraction decreased to 2 percent (Fig. 4). During the recovery period after atrial pacing, the chest pain gradually diminished and disappeared by 5 minutes. Left ventricular end-diastolic pressure slowly declined but was abnormally elevated until 5 minutes into the recovery period. Myocardial lactate extraction returned to near normal after 5 minutes of recovery. The values for glucose and free fatty acid extraction showed no significant alteration (Table II), and the arterial and coronary sinus values for pH

TABLE II

Myocardial Substrate Data

	Control (65/min)	Pacing (136/min)	Pacing (146/min)	Recovery (5 min) (71/min)
Lactate (mmoles/liter)				
Art	0.961	0.875	0.658	0.464
CS	0.453	0.442	0.648	0.279
FFA (μmoles/liter)				
Art	450	434	473	545
CS	403	419	391	435
Glucose (mg/dl)				
Art	102	124	120	130
CS	80	77	86	79

Art = arterial; CS = coronary sinus; FFA = free fatty acids.

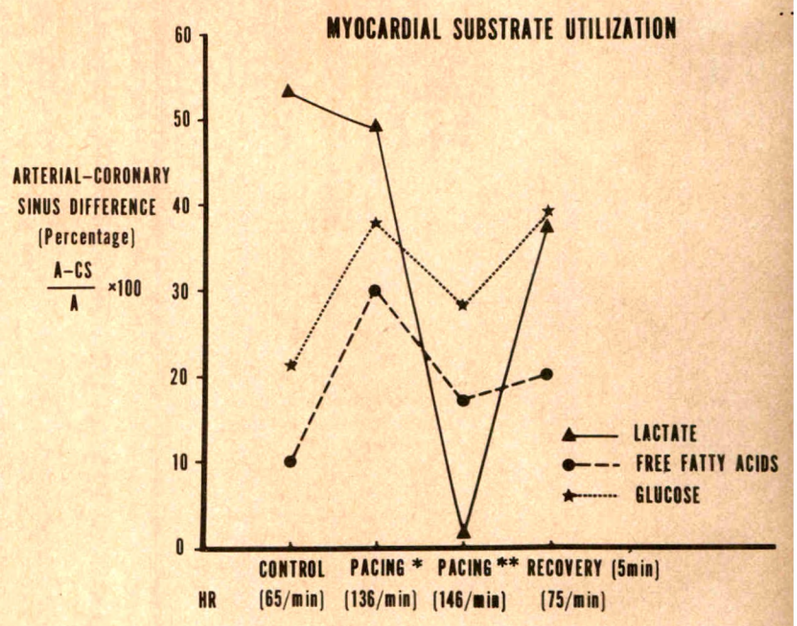


FIGURE 4. Graph of lactate, free fatty acid and glucose arterial-coronary sinus difference with atrial pacing study. The decrease in lactate arterial-coronary sinus difference (to 2 percent) at a pacing rate of 146/min was associated with severe chest pain. A = arterial; CS = coronary sinus; HR = heart rate; * = mild chest pain; ** = severe chest pain.

and partial pressures of oxygen and carbon dioxide were normal and did not change throughout the pacing study.

Discussion

Chest pain suggestive of angina pectoris in patients with normal coronary arteriograms is well recognized, and may be seen in as many as 30 percent of patients undergoing coronary arteriography for suspected coronary artery disease,[4] and in nearly 10 percent of patients with typical exertional chest pain.[5] Similar chest pain is often found in patients with the mitral valve prolapse syndrome, and its origin is usually not clear.[6] These patients, in addition, often have electrocardiographic changes suggesting ischemia[7] and abnormal treadmill exercise responses[8] indistinguishable from those seen in patients with significant coronary artery disease. Hemodynamic[9] and myocardial metabolic[10,11] abnormalities with atrial pacing have been documented in patients with angina and normal coronary angiograms, and similar hemodynamic and metabolic studies with atrial pacing have demonstrated abnormal lactate responses in up to 30 percent of selected patients with chest pain and mitral valve prolapse.[12,13] Although the significance of and basis for these findings remain unclear, myocardial ischemia has been strongly implicated.

Mitral valve prolapse is now recognized as a common clinical entity[6,7] and prolapse may involve both A-V valves in the same patient. The finding of bilateral A-V valve prolapse has been reported in up to 50 percent of patients with mitral valve prolapse who have right ventricular angiography[14,15] or echocardiographic visualization of the tricuspid valve.[16] In addition, an association between A-V valve prolapse and certain forms of congenital heart disease has been noted. Mitral valve prolapse has been reported to occur with increased frequency in patients with atrial septal defect[17,18] and has recently been reported by Roberts et al.[19] in two patients with Ebstein's anomaly of the tricuspid valve.

Association of corrected transposition and bilateral A-V valve prolapse: Anatomically corrected transposition of the great vessels is uncommon, and its occurrence as an isolated finding (in the absence of intracardiac shunts, pulmonary outflow tract obstruction, heart block or left A-V valve regurgitation) is rare.[20] Abnormalities of the left A-V valve in corrected transposition are known to occur and are usually due to an Ebstein-type malformation[21] with displacement of the septal leaflet into the systemic ventricle. In a pathologic study of the pulmonary outflow tract in classically corrected transposition, Anderson et al.[22] observed herniation of a fibrous tag of an inverted tricuspid valve through a ventricular septal defect into a pulmonary outflow tract and considered it a possible cause of pulmonary outflow tract obstruction. However, the occurrence of bilateral or left A-V valve prolapse in isolated corrected transposition has, to our knowledge, not been described previously. In addition, our patient had severe disabling chest pain indistinguishable from unstable angina pectoris. Chest pain may occur in isolated corrected transposition, and Dodek and Neill[1] described a patient with corrected transposition who had chest pain over a 20 year period masquerading as coronary artery disease. This patient had normal coronary arteries on arteriography, and angiographically mild "mitral" and aortic valve regurgitation.

Possible causes of ischemia in absence of coronary disease: The cause of chest pain in our patient is not known. Its character, response to nitroglycerin and reproduction with atrial pacing are characteristic of angina pectoris, and the strikingly abnormal clinical, metabolic and hemodynamic response to atrial pacing suggest "ischemic" myocardial dysfunction. The

mechanisms involved may be similar to those responsible for the as yet poorly understood syndrome of "angina with normal coronary arteriograms." In addition, a possible relation between the chest pain and the clinical and angiographic evidence of A-V valve prolapse in this patient must also be considered, and the rarity of either in corrected transposition of the great vessels might indicate a more than fortuitous association. The anatomically corrected transposition may be an incidental finding. Nevertheless, it is possible that the systemic (morphologic right) ventricle and its associated coronary arterial system are structurally inadequate to function normally at systemic arterial pressures for an extended period of time. To our knowledge no similar case has been reported. This case adds to the widening spectrum of chest pain with normal coronary arteriograms and to the variety of abnormalities that may be seen with corrected transposition of the great vessels.

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Isolated Ventricular Discordance and Complete Atrioventricular Canal in Situs Inversus

Report of Successful Surgical Repair

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Isolated ventricular discordance is a very rare malformation, most often lethal in the first months of life. A patient with this lesion survived to age 9 years in spite of the coexistence of a complete form of atrioventricular (A-V) canal. Surgical repair with a Mustard procedure was associated with correction of the endocardial cushion defect. Situs inversus itself caused no problem. Although permanent complete A-V block occurred, the result has been satisfactory so far. This case is thought to be the first successful correction of this malformation.

Isolated ventricular discordance is a rare cardiac malformation in which the right atrium opens into a morphologically left ventricle through a mitral-shaped orifice. The aorta arises from this ventricle. On the other side of the heart, the arterialized blood proceeds from the left atrium to a morphologically right ventricle, and then to the pulmonary artery. Blood circulation is the same as in transposition of the great arteries. We recently had the opportunity to operate on a patient who had this malformation with a complete form of atrioventricular (A-V) canal and situs inversus.

Case Report

The patient was a 9 year old girl with poor physical development (16 kg, 124 cm). Episodes of bronchitis had been frequent since birth. Physical examination revealed slight cyanosis with clubbing but no signs of cardiac failure. The cardiac apex was right-sided. A grade 4/6 systolic murmur was heard at the fourth right intercostal space. The second heart sound was accentuated. A spleen was present, and no Howell-Jolly bodies could be found. X-ray examination showed a right-sided stomach bubble and dextrocardia with marked cardiac enlargement and increased vascular markings (Fig. 1). The electrocardiogram confirmed the situs inversus with negative P waves in lead I. Rhythm was either sinus or junctional at about 60 beats/min with frequent ventricular escape beats. The QRS axis was −120°.

Cardiac catheterization was performed in April 1973. There was an azygos continuation of the left-sided inferior vena cava to a left-sided superior vena cava. The atrium, entered from the venous approach, was left-sided. Systolic pressures were equal in both ventricles and in the aorta (120 mm Hg) and were somewhat lower in the pulmonary artery (80 mm Hg). Oximetry findings were not conclusive because oxygen saturation was almost the same in all cardiac chambers (between 83 and 89 percent).

Angiography was performed with use of a venous catheter (Fig. 2, A and B). Across a large atrial septal defect dye was injected into a right-sided ventricle that was trabeculated and gave rise to an anterior and markedly dilated pulmonary artery. A second injection, using an arterial retrograde catheter (Fig. 2, C and D), opacified a morphologically left ventricle located to the left of and anterior to the first ventricle and giving rise to a small and posteriorly placed

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aorta. The pulmonary artery was faintly opacified with this injection, but a ventricular septal defect was not clearly delineated. The preoperative diagnosis was ventricular inversion with ventricular and atrial septal defects as well as kinetic pulmonary hypertension.

Surgical repair: Operation was performed in June 1974 through a median sternotomy. The position of the atria was typical for situs inversus (Fig. 3). The aortic anulus was located posteriorly and to the left. The ascending aorta was small and to the right. The pulmonary artery was greatly dilated and in an anterior position; it arose from a right-sided ventricle through a well formed infundibulum.

Under cardiopulmonary bypass, the anterior atrium which received the venae cavae was opened vertically and the anatomic features inspected. There was no interatrial septum. This single atrium was part of a complete form of A-V canal. There was an anterior and a posterior common A-V leaflet between which the sagittal interventricular septum had a 5 mm free border. The anterior common leaflet was attached to the interventricular septum by short chordae tendineae; a small ventricular septal defect in this area resulted from incomplete coalescence of the chordae. The posterior common leaflet floated freely above the septum, thereby resulting in a large ventricular septal defect (Rastelli's type A). The papillary muscles and the lateral leaflet of the anterior ventricle were of a mitral configuration. Similarly, the papillary muscles and the lateral leaflets of the posterior ventricle were of a tricuspid configuration.

The first stage of the repair dealt with the A-V canal, and the technique described by Rastelli et al.[1] was employed. The anterior and posterior A-V leaflets were approximated with interrupted sutures and then divided following the plane of the interventricular septum. This section exposed both ventricular septal defects. A Dacron® patch was inserted on the superior edge of the interventricular septum, with its anterior part along the right border of the aortic ring. Suture of the patch was extended for 10 mm into the common atrium in order to create the equivalent of a septum primum. The median edges of both mitral and tricuspid septal leaflets were attached to the patch, the mitral a few millimeters higher than the tricuspid, in order to avoid obstruction of the left ventricular outflow tract. An intraatrial Dacron baffle was then inserted, first around the orifices of pulmonary veins and then around the orifices of both venae cavae. Its ventral border was sutured to the free edge of the patch used for repair of the A-V canal (Fig. 4). There was no distinct orifice for the coronary sinus, and the multiple cardiac veins were diverted to the caval side of the baffle. Bypass was discontinued without difficulty, although complete A-V block necessitated pacing with two temporary epicardial electrodes. The following pressures (in mm Hg) were measured: subaortic ventricle 90/5, aorta 90/60, subpulmonary ventricle 60/5 and pulmonary artery 50/20.

The immediate postoperative course was uneventful. The A-V block persisted with a ventricular rate of approximately 70/min. This block was poorly tolerated even though an intermittent junctional rhythm had often produced the same rate before operation. A permanent pacemaker was inserted by way of an epigastric approach on the 20th postoperative day and the child was then discharged without further major problems. Two years postoperatively, in June 1976, there was no sign of cardiac failure and heart volume had decreased. Her general condition was good and her physical capacity had progressively improved since operation.

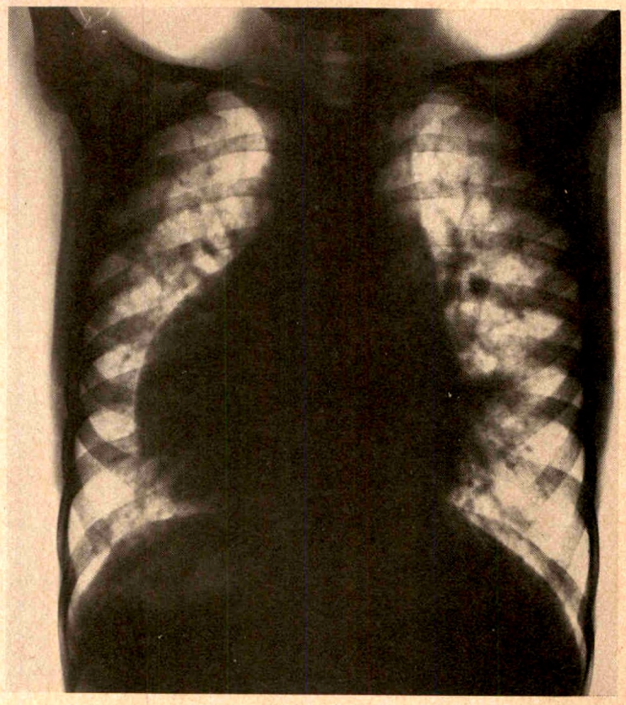


FIGURE 1. Preoperative chest roentgenogram. Note cardiac enlargement, right-sided stomach bubble, dextrocardia and increased pulmonary vascular markings.

Discussion

In 1966, Van Praagh and Van Praagh[2] first used the term "isolated ventricular inversion" when reporting a case they believed to be the second one published (the first had been reported by Lev and Rowlatt[3]). Our case was first termed "isolated ventricular inversion in situs inversus," following the example of Espino Vela et al.[4] But this term is ambiguous, because in total situs inversus, ventricles are inverted by definition. Therefore the correct term should be "isolated ventricular *non-inversion* in situs inversus," which is confusing. The term "isolated ventricular discordance," suggested by Van Praagh,[5] is valid in both situs solitus and situs inversus.

According to the segmental approach, our case may be classified as situs inversus,[2] right bulboventricular loop (D) and normally related great vessels vis à vis the chambers from which they arise (S). This "normal" interrelation of the great vessels in situs inversus is exceedingly rare.[5,6] In our patient both the ventricular and the conotruncal segments are discordant with the visceroatrial situs, namely, situs inversus.

The prognosis of this kind of malformation is obviously poor in infancy. Recently, Quero Jimenez and Raposo-Sonnenfeld[7] found only four reported cases of isolated ventricular inversion, to which they added two personal cases. All of the patients were infants and all died between the ages of 12 days and 7 months. Preoperative diagnosis was achieved in only two cases: Those two patients were unsuccessfully operated on (Blalock-Hanlon procedure in one and banding of the pulmonary artery in the other). This poor prognosis is probably related to the large incidence of small morphologically right ventricles and to left A-V valve ob-

structions.[7] In our case, none of these additional malformations was present.

Surgical treatment of this malformation is the same as that in the usual transposition of great arteries: the rerouting of blood through the atria with a Mustard procedure. The presence of a complete form of A-V canal is not a surgical problem in itself, since the treatment of this malformation has been codified.[1] Nevertheless, the performance of a Mustard operation and abolition of the A-V canal are not simply the result of juxtaposition of the two distinct procedures because in this case there is no interatrial septum on which the ventral border of the baffle can be inserted. In our case the patch used for the A-V canal repair was left 1 cm too long dorsally, and this extra length constituted the equivalent of a septum primum. The ventral border of the baffle was sutured to the edge of the patch used for the A-V canal repair.

The occurrence of postoperative A-V block has two possible explanations: (1) Ventricular inversion is commonly associated with an abnormal location of conductive tissue. (2) Absence of a distinct coronary sinus ostium makes the Mustard procedure technically dangerous for the A-V node and the bundle of His. In such complicated cases, mapping of the conductive tissue at operation may be very helpful because it is impossible to predict location of the tissue from the usual anatomic landmarks.

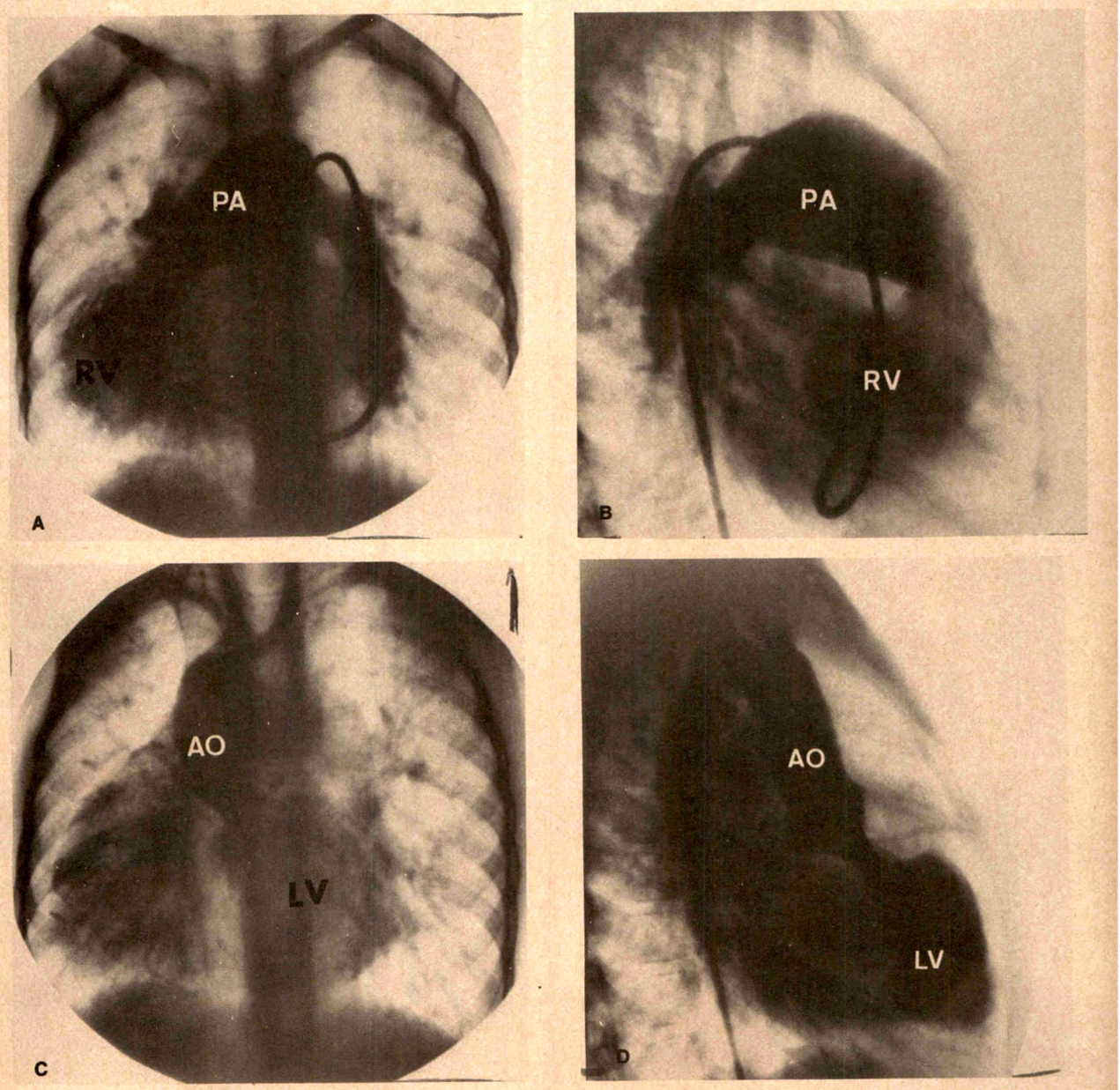


FIGURE 2. Selective angiocardiograms of the morphologically right ventricle (RV) (**A** and **B**) and the morphologically left ventricle (LV) (**C** and **D**). The diagnosis of A-V canal should have been suspected from view **D** (gooseneck appearance and scalloping along the posterior border of the left ventricular outflow tract, cleft in the mitral portion of the common A-V valve). PA = pulmonary artery; AO = aorta.

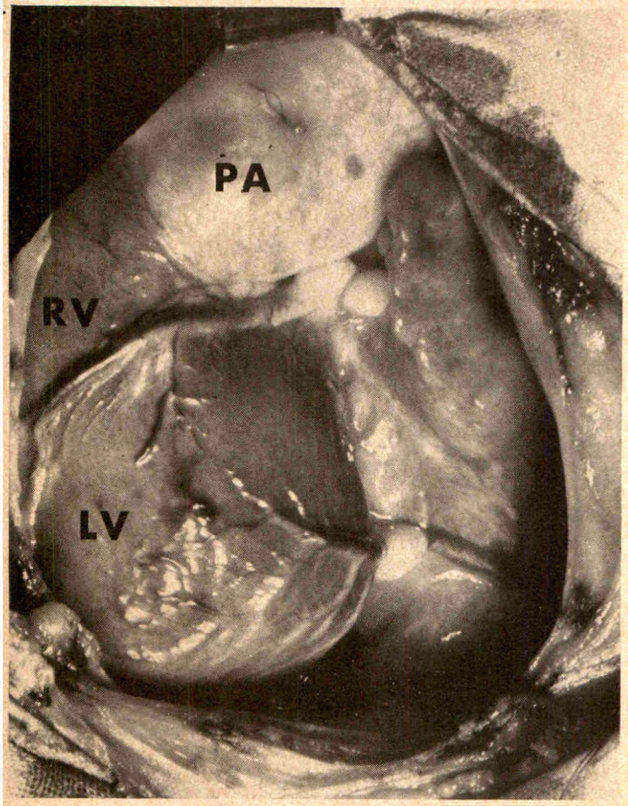


FIGURE 3. Operative view of the heart through median sternotomy. The left ventricle (LV) is anterior and located on the left. The huge pulmonary artery (PA) is anterior to the ascending aorta, which is posterior and right-sided and cannot be seen in this view. RV = right ventricle.

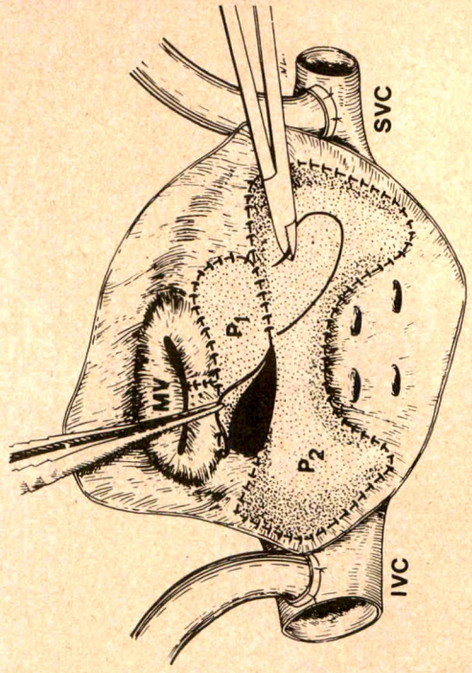


FIGURE 4. Schematic drawing of the technique of repair. The ventral edge of the Mustard patch (P_2) is sutured to the dorsal edge of the patch used for the repair of the A-V canal (P_1). IVC and SVC = inferior and superior venae cavae; MV = mitral valve.

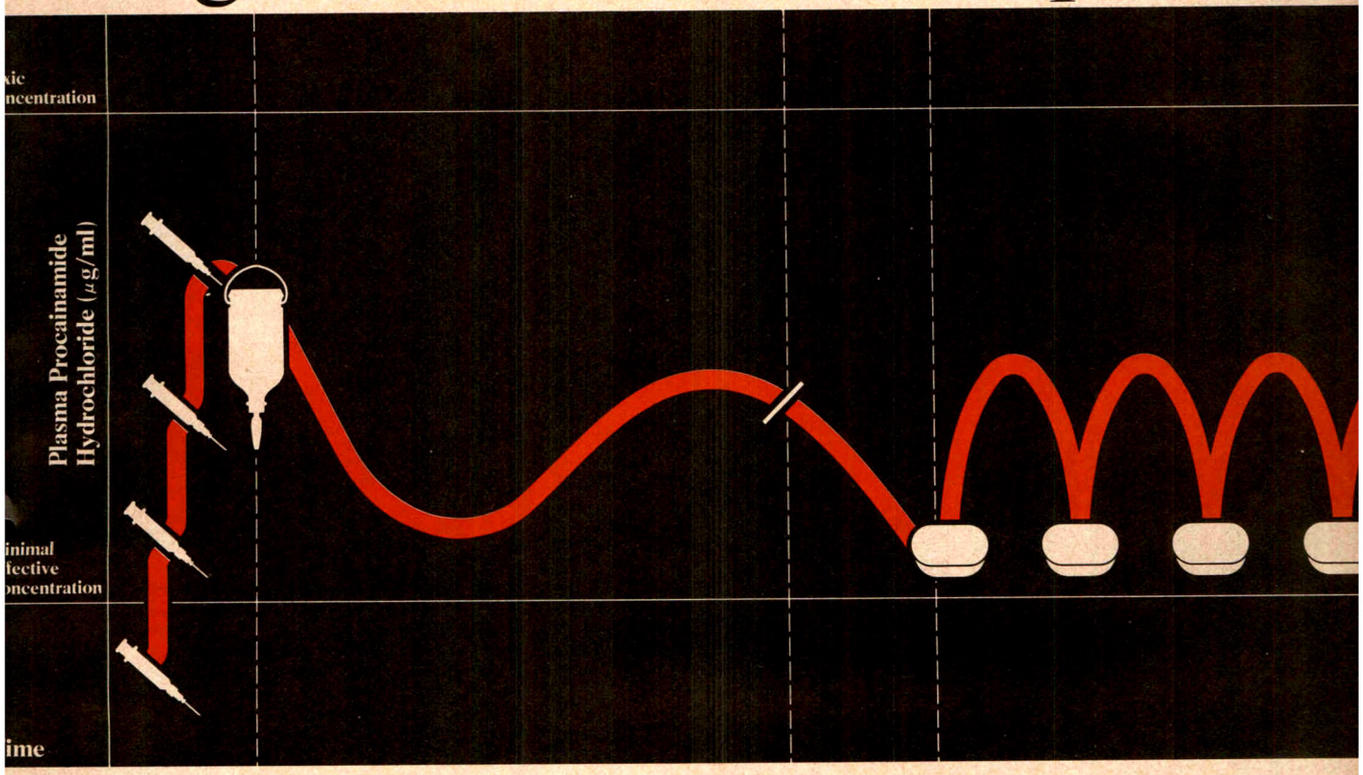
Acknowledgment

We are greatly indebted to Dr. Richard Van Praagh for helping us in the understanding of this case.

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A syndrome resembling lupus erythematosus has been reported with main- ance procainamide therapy. Common symptoms are polyarthralgia, arthritis pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis y also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic mia, possibly related to this syndrome, have been reported. Measure anti- lear antibody titers at regular intervals in patients on procainamide for ended periods of time or in whom symptoms suggestive of lupus-like reaction ear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, ss the benefit/risk ratio related to continued procainamide therapy (see ed Warning). Steroid therapy may be effective if discontinuation of pro- ıamide does not cause remission of symptoms. If the syndrome develops in a ient with recurrent life-threatening arrhythmias not otherwise controllable, oid-suppressive therapy may be used concomitantly with procainamide.

VERSE REACTIONS: Hypotension is rare with oral administration. Serious urbances of cardiac rhythm such as ventricular asystole or fibrillation are re common with I.V. administration.

arge oral doses may sometimes produce anorexia, nausea, urticaria, and/or ritus.

A syndrome resembling lupus erythematosus has been reported (see Precau- ıs). Reactions consisting of fever and chills have been reported, including a e with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in um glutamic oxaloacetic transaminase following single doses of the drug. anulocytosis has been occasionally reported following repeated use of the g, and deaths have occurred. Therefore, routine blood counts are advisable ing maintenance procainamide therapy; and the patient should be instructed eport any soreness of the mouth, throat, or gums, unexplained fever or any ıptoms of upper respiratory tract infection. If any of these symptoms should ur and leukocyte counts indicate cellular depression, procainamide therapy uld be discontinued and appropriate treatment should be instituted im- diately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psy- sis with hallucinations, and hypersensitivity reactions such as angioneurotic ma and maculopapular rash have been reported.

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CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial response should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

ADMINISTRATION: Oral administration is preferred. When parenteral therapy is necessary, intramuscular administration is the method of choice. *Intravenous use should be limited to extreme emergencies,* **the drug should be administered as a dilute infusion,** and the patient should be monitored electrocardiographically. The intravenous dose should not exceed 1 gram. Administer at a rate not exceeding 25 to 50 mg. per minute.

Should procainamide therapy be continued for any appreciable period, electrocardiograms should be made occasionally to determine its further need.

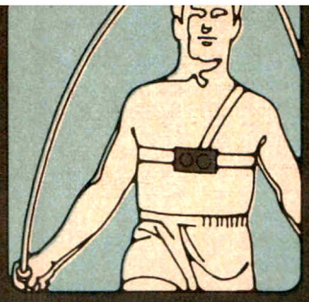
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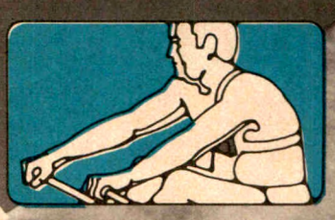
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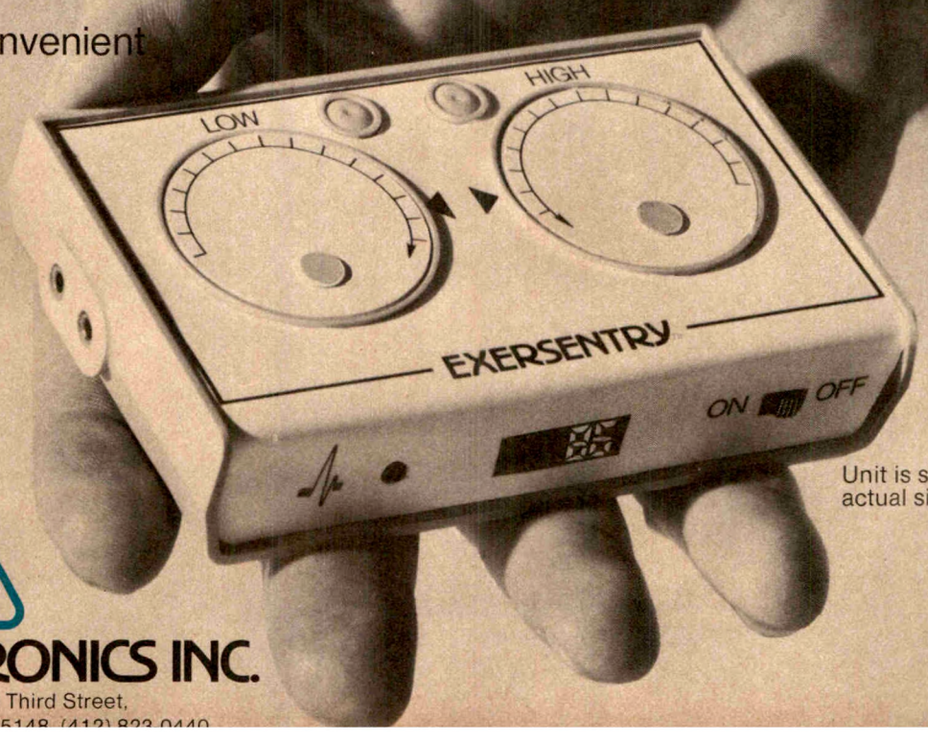






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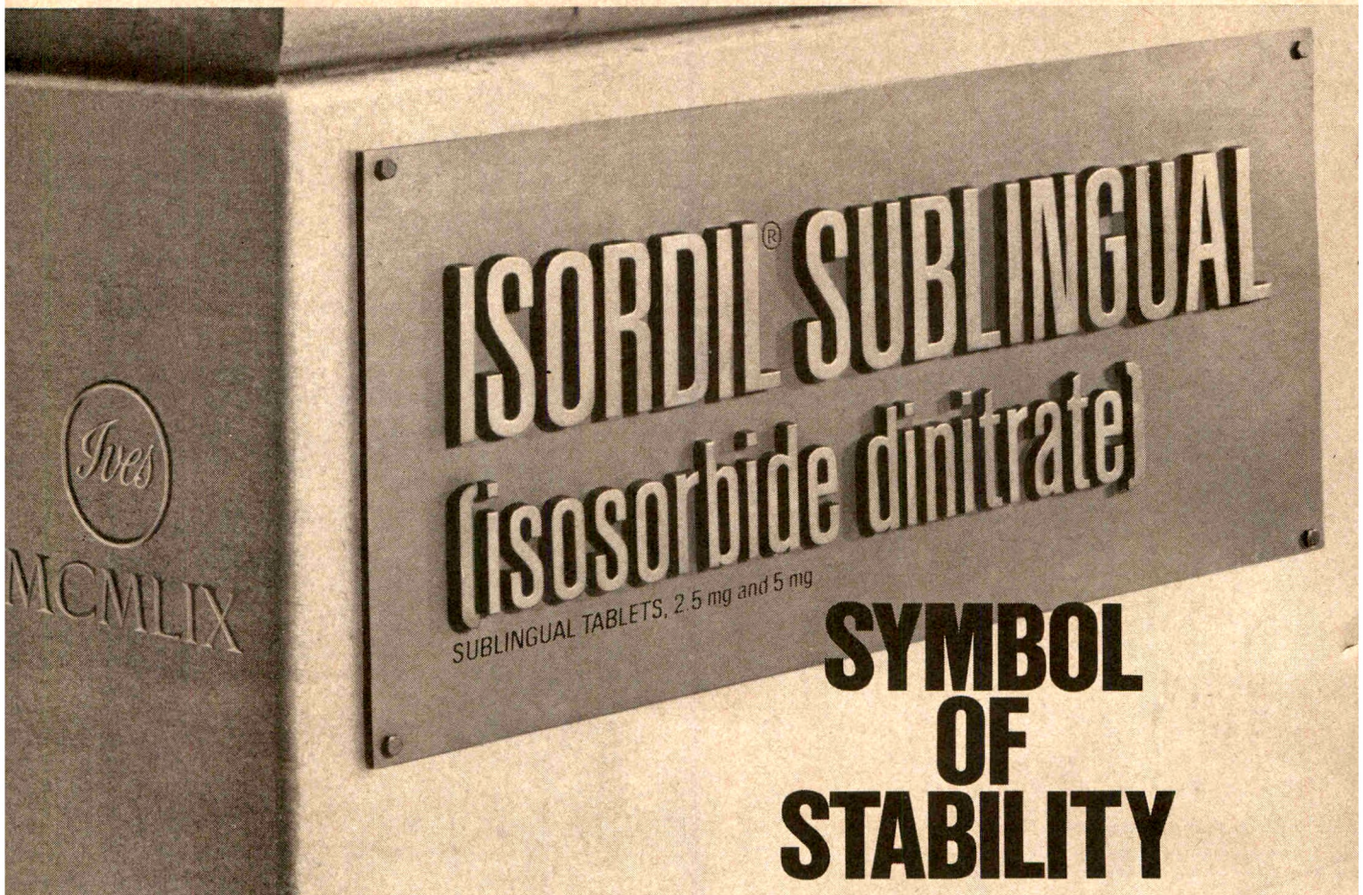
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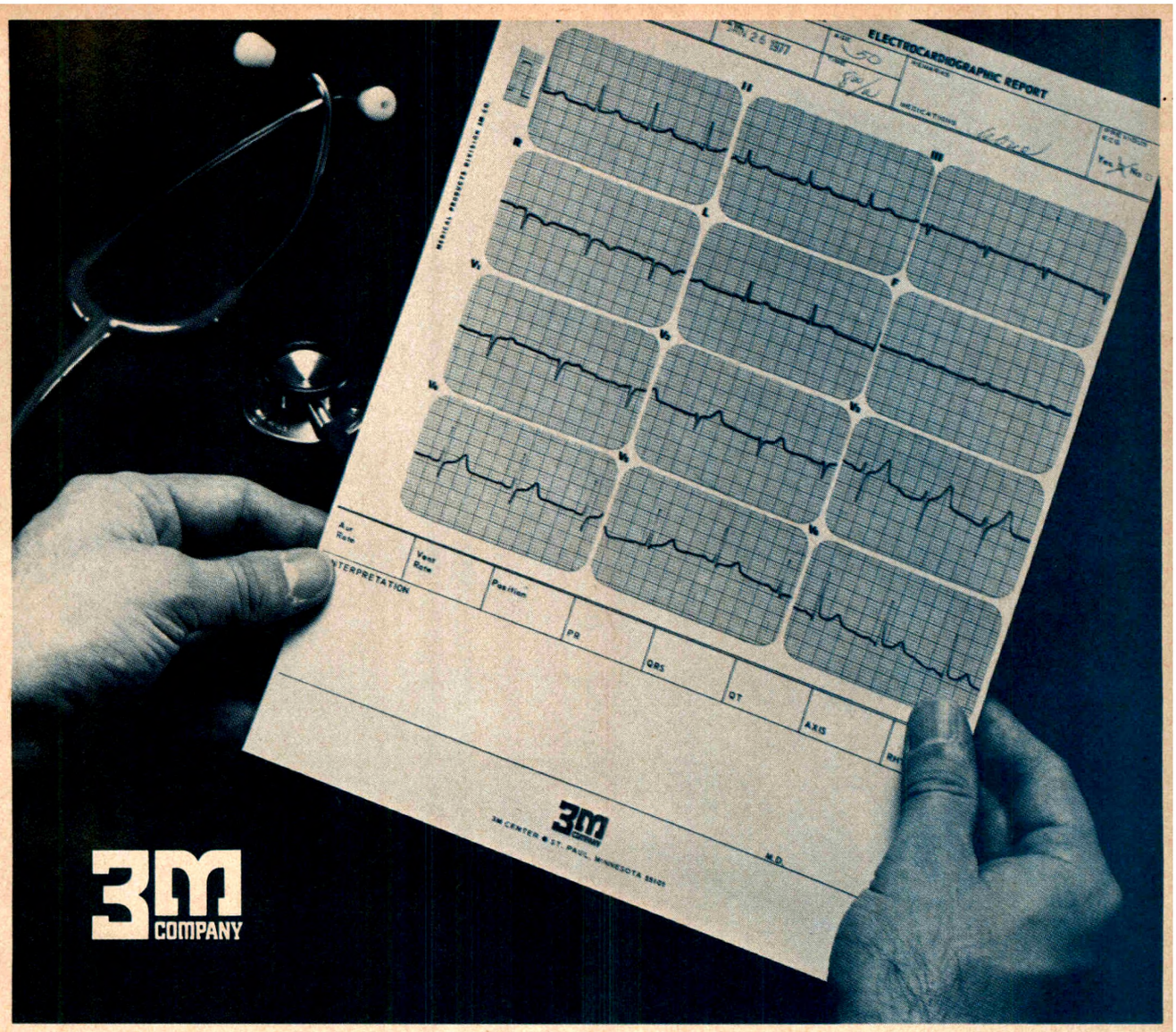
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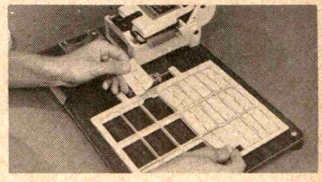
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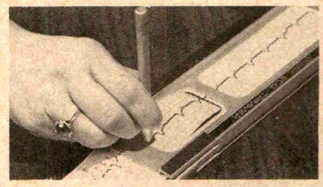
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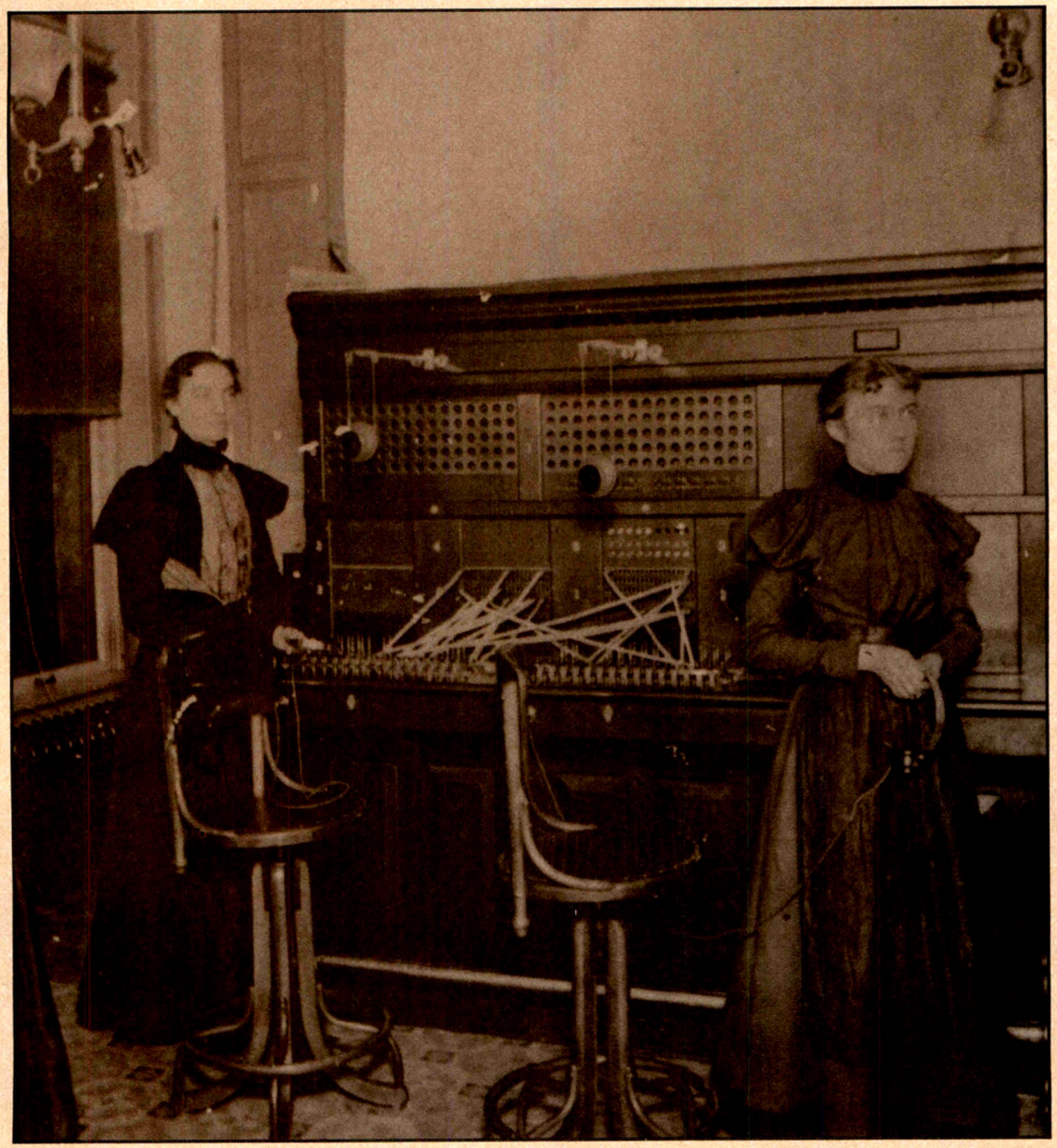
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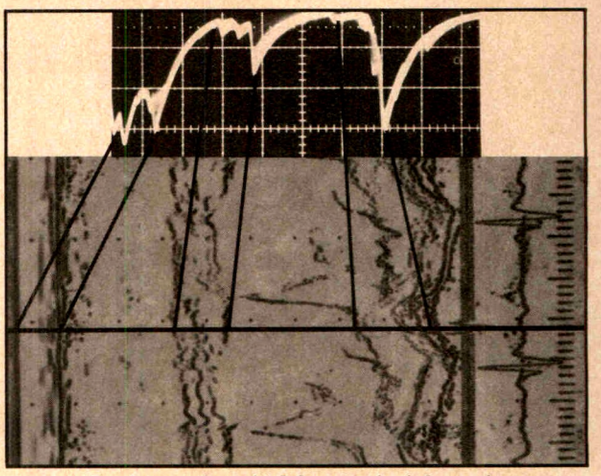
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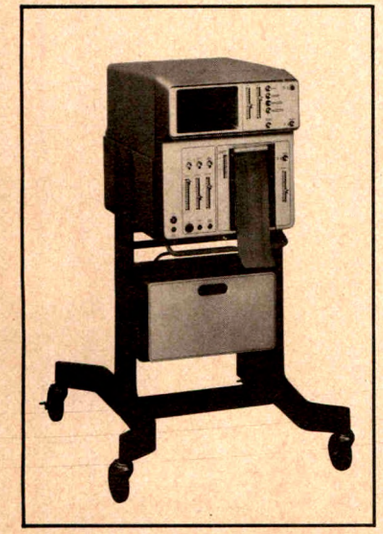


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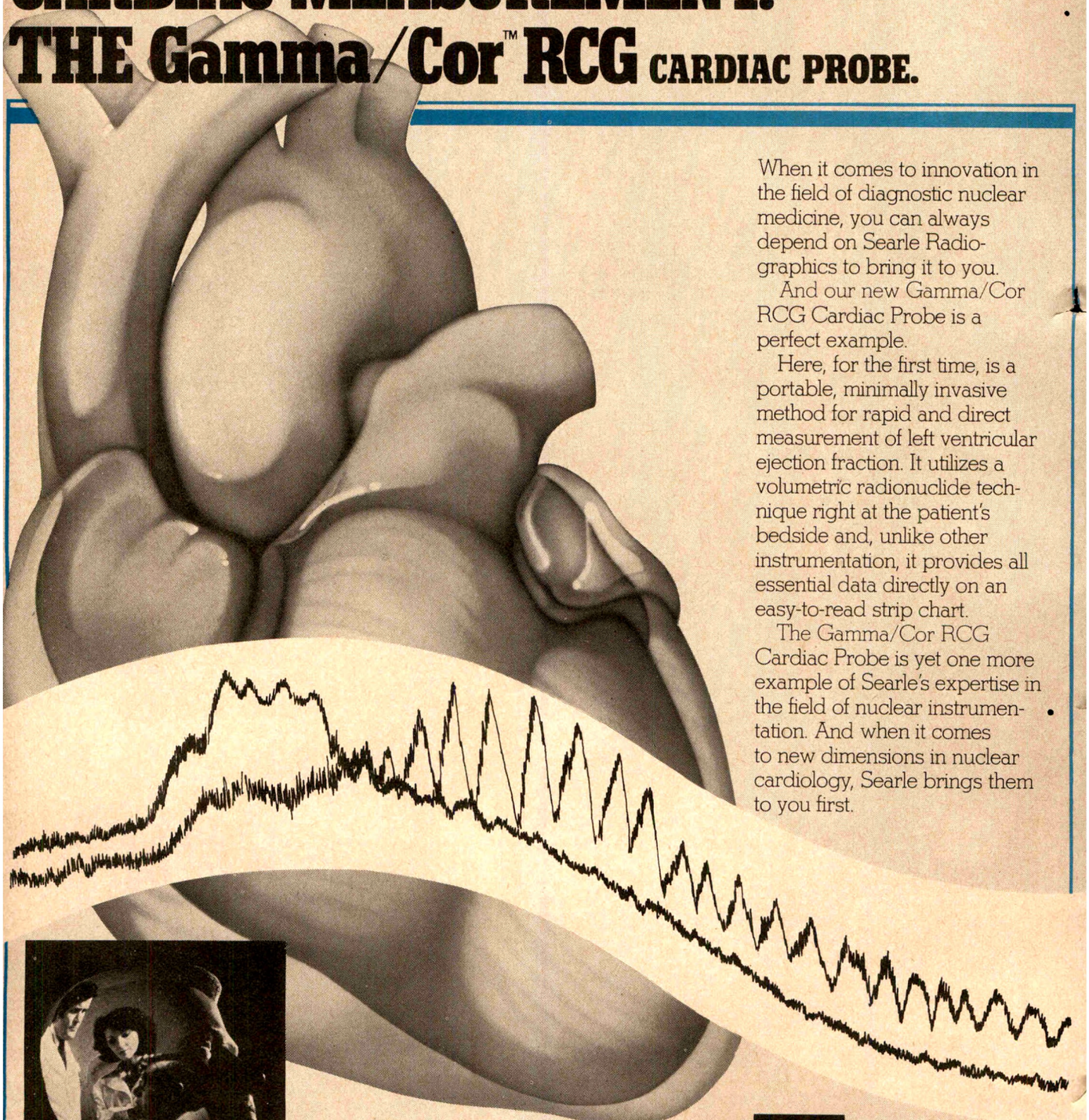
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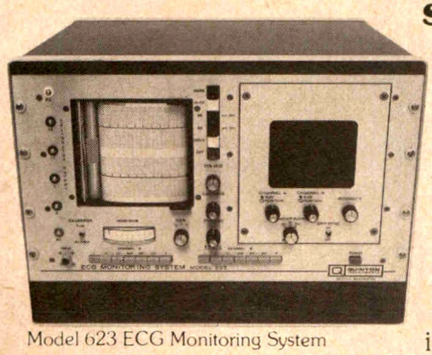


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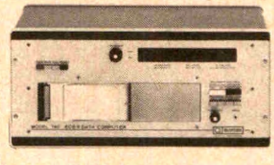
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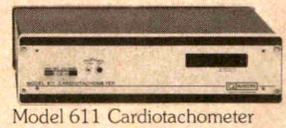


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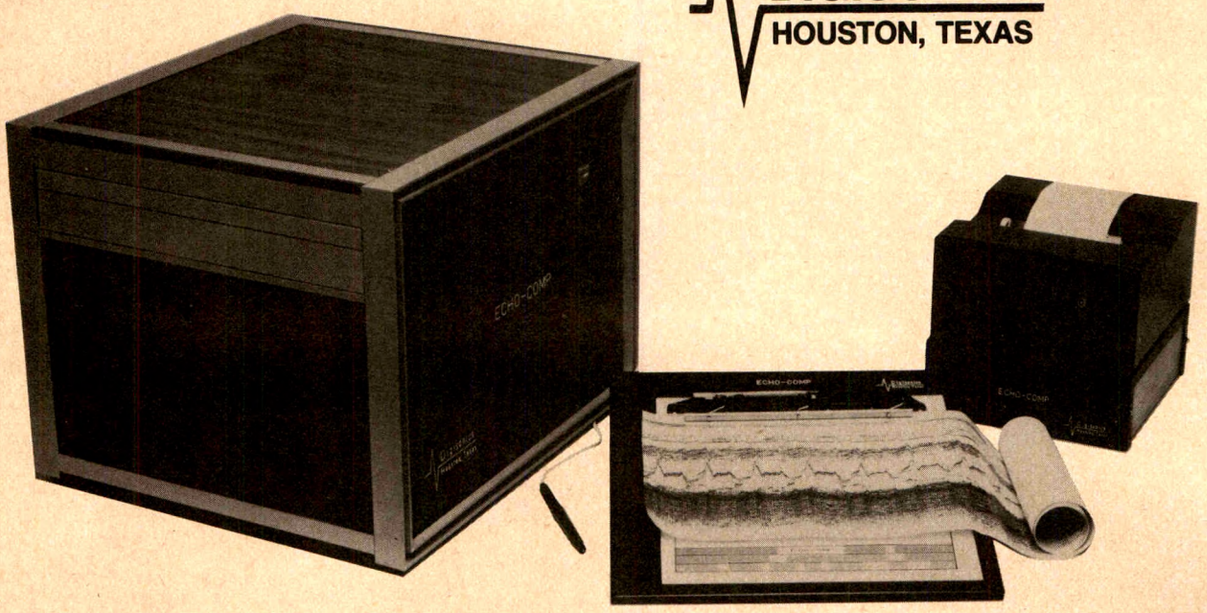
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Mechanism of Early "Pump" Failure of the Ischemic Heart: Possible Role of Adenosine Triphosphate Depletion and Inorganic Phosphate Accumulation*

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Interruption of coronary flow to a portion of the heart leads to a decline in contractility that causes the ischemic myocardium to fail to participate in the generation of intraventricular pressure, and instead to bulge outward during systole.[1] The mechanism that initiates this early "pump" failure remains poorly understood. In spite of the many advances in our understanding of the effects of ischemia on intermediary metabolism[2–5] and of the mechanisms that control myocardial contractility,[6–8] the way in which ischemia initiates a signal that causes myocardial contractility to decrease remains a mystery. Hypotheses regarding this causative mechanism have been brought forward, but none provides an unambiguous explanation for this important phenomenon. We shall examine several possible mechanisms linking an interruption of coronary blood flow to loss of myocardial contractile function. Although none provides an unequivocal answer to this question, we hope that the findings and concepts to be reviewed will both aid in the understanding of currently available data and promote additional studies of these important phenomena.

From the Medizinische Universitäts-Klinik, Abteilung Innere Medizin III (Kardiologie) and the Max-Planck Institut für Medizinische Forschung, Abteilung Physiologie, Heidelberg, West German Federal Republic; and the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine of the City University of New York, New York. Manuscript received December 13, 1976; revised manuscript received March 23, 1977, accepted March 23, 1977.

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A large body of experimental evidence provides a good understanding of both the initial and final events in the chain of events that link an interruption of coronary blood flow to a decline in myocardial contractility. The initial event that causes myocardial contractility to decline in the ischemic heart is almost certainly lack of oxygen, which results from a decrease in myocardial oxygen tension.[9] Although significant differences exist between the myocardial responses to ischemia and anoxia,[3,4,10] both cause a rapid decline in myocardial contractility. Although failure of perfusion adds to the detrimental effects of lack of oxygen, mainly through the inability of the ischemic myocardium to rid itself of some important metabolites—notably hydrogen ion and lactate,[3,4,11] our discussion focuses on the loss of contractility that occurs almost as rapidly in the anoxic myocardium as it does in ischemia.

Lack of adenosine triphosphate and myocardial contractility: There is now abundant evidence that within a few seconds after blood flow to a region of the heart is interrupted, myocardial oxygen tension decreases almost to zero,[9] causing a virtual halt in aerobic energy production. Cessation of oxidative phosphorylation in the ischemic regions is accompanied by a marked initial decrease in the content* of phospho-

* The term *content*, as used in this article, defines the amount of substance per unit weight of tissue (for example, μmoles per gram of wet weight), whereas *concentration* is the amount of a substance present per unit volume of the space in which it is distributed (for example, μmoles per liter of cell water, or μmoles per liter of a compartment within the cell).

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

[redacted]ut only a modest decrease in adenosine triphosphate (ATP) content at the same time that myocardial contractility decreases precipitously.[12] Because phosphocreatine can provide energy for cell function only by transferring high energy phosphate first to ATP, it seems reasonable to attribute the early "pump" failure of the ischemic heart to lack of ATP for a critical reaction in the mechanisms that control the contractile process.

Perhaps the simplest explanation for the early "pump" failure of the ischemic heart is that the unavailability of ATP halts the critical energy-consuming reactions associated with the contractile process. This view might, at first glance, appear to be untenable because of the finding that the ATP *content* of the ischemic myocardium decreases only 10 to 20 percent at a time when contractility has fallen to very low levels.[12,13] This apparent discrepancy would appear to be especially significant because relatively small *concentrations* of ATP are required to saturate the substrate-binding sites of several well studied energy-consuming processes involved in the regulation of myocardial contractility. For example, both the contractile proteins and the known ion pumps involved in the control of myocardial contraction are half saturated at ATP *concentrations* in the range well below 0.1 mmole/liter.[6,14,15] Yet, the ATP *content* of the ischemic myocardium immediately after coronary occlusion is more than 3 μmoles/g wet weight. If this ATP were distributed uniformly throughout the myocardial cell water, which constitutes approximately 70 percent of its wet weight, ATP *concentration* would be over 4 mmoles/liter, a level that would virtually saturate the ATP-binding sites discussed. In view of evidence that ATP concentrations are not the same in all parts of the myocardial cell, and that ATP concentration decreases markedly in certain areas or "compartments" in the ischemic myocardial cell, this quantitative argument cannot exclude the possibility that lack of ATP itself causes the early "pump" failure of the ischemic heart.

Compartmentalization of ATP in the ischemic heart: Strong evidence that ATP levels drop precipitously in specific compartments of the ischemic myocardium stems from the accepted view that phosphocreatine (PC) is formed and degraded only through transfer of high energy phosphate from or to ATP according to the reaction: PC + ADP ⇌ C + ATP (where C = creatine). The relation between concentrations of phosphocreatine and creatine, and of ATP and adenosine diphosphate (ADP), is governed by the equilibrium for the enzyme creatine kinase. The mass action ratio: [PC] times [ADP] divided by [C] times [ATP] yields an equilibrium constant, K, defined in equation 1, of approximately 0.01.[5]

$$\frac{[PC]\,[ADP]}{[C]\,[ATP]} = K = 0.01 \qquad (1)$$

Measured myocardial contents of phosphocreatine, ADP, creatine and ATP would, if they represented true concentrations, be expected to yield the appropriate equilibrium constant. However, values for these apparent mass action ratios obtained under aerobic conditions in the canine myocardium are far from those predicted by the equilibrium constant.[3,5,13,16,17] This discrepancy does not appear to reflect a difference between the properties of creatine kinase in the intact heart and those defined by studies of the enzyme in vitro because, in the anoxic perfused and ischemic heart, after phosphocreatine levels decline to low values the mass action ratio reaches and is maintained at the equilibrium predicted by equation 1.[16,17]

The finding that cell phosphocreatine content can change independently of the rate of change of ATP content—for example, during the metabolic response to changing levels of cardiac work[5,16]—provides further evidence that high energy phosphate compounds are compartmentalized in the heart. In the ischemic heart as well, phosphocreatine content falls more rapidly and to a proportionately much greater extent than does the cell content of ATP (see earlier). These findings can readily be explained if only a portion of the cell ATP content is in equilibrium with most or all of the cell phosphocreatine in a discrete compartment within the myocardial cell, and if hypoxia and ischemia cause a marked fall in ATP concentration within this compartment.

Effects of depletion of ATP as substrate in the ischemic heart: rigor versus decreased contractility: Even if the hypothesis set forth in the preceding paragraphs is correct, and ischemia causes a marked decline in ATP concentration within a critical cell compartment, considerable difficulty remains in providing an explanation for the early "pump" failure of the ischemic heart. This difficulty arises because lack of ATP as substrate for the known energy-consuming reactions associated with the regulation of myocardial contractility would, according to present understanding, lead to rigor rather than to the decrease in myocardial contractility seen initially in the ischemic heart.[18] Lack of substrate for the contractile proteins would cause the myofibrils to go into rigor,[6] whereas inhibition of the calcium pump of the sarcoplasmic reticulum by substrate lack would, by preventing the removal of this ion from the region of the cell occupied by the contractile proteins, also promote rigor. Inhibition of the sodium pump would tend to increase intracell calcium concentration because, according to known mechanisms, the resulting accumulation of sodium in the region of the cell just beneath the sarcolemma would tend to decrease calcium efflux from the cell.[7] Although evidence for a sarcolemmal calcium pump is scanty, lack of energy for such a calcium pump would also lead to rigor because ATP-dependent transport of calcium out of the cell would be inhibited. Finally, a lack of energy for mitochondrial ion transport would also tend to promote rigor by reducing calcium transport into these cell organelles. For these reasons, it remains difficult to explain the mechanism by which a marked decline in ATP concentration in one or more regions of the myocardial cell could lead *directly* to the loss of contractility seen in the ischemic heart.

TABLE I

Predicted Changes in High Energy Phosphate Levels Caused by a 75 Percent Decline in Phosphocreatine Levels in the Cardiac Cytosol

	PC	C	ATP	ADP	AMP	P
Initial level	21.8	11.2	9.7	0.05	0.00028	5.6
Final level	5.5	27.5	1.0	0.05	0.00275	48.0
P liberated	+16.3	—	+26.1*	—	(−0.00247)	+42.4

* 26.1 = 3 × 8.7 because each mole of ATP contains 3 moles of P.

All values are mmoles per liter cytosol water.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; C = creatine; P = phosphate; PC = phosphocreatine.

Possible effects of loss of modulatory function of ATP in the ischemic heart: In addition to providing chemical energy for the contractile process and for ion pumps, ATP appears to have important modulatory effects on the processes that control myocardial cell function. In addition to the well known ability of ATP to modulate energy production, manifested for example in the regulation of the enzyme phosphofructokinase, this nucleotide can also affect passive ion fluxes. The ability of ATP to promote ion exchange by the erythrocyte membrane has recently been shown in the case of potassium:potassium exchange to be independent of the ability of the nucleotide to provide energy for chemical reactions.[19] Similarly, ATP can promote sodium:calcium exchange in the squid axon by a mechanism that appears, at least in part, to be independent of its ability to serve as substrate for energy-consuming reactions.[20,21] These modulatory actions of ATP appear to require levels of this nucleotide in the range between 0.1 and 1.0 mmole/liter,[20] which is considerably higher than that needed to saturate the substrate-binding sites for energy-consuming reactions (see preceding).

The possibility that these modulatory effects of ATP may contribute to the early "pump" failure of the ischemic heart is suggested by the finding that metabolic poisons reduce the entry of calcium into the myocardium by way of the slow channel[22,23] and that passive calcium efflux from the sarcoplasmic reticulum is greatly reduced in the absence of ATP.[24] Although evidence to support this hypothesis is still scanty, the modulatory role of ATP represents an important area for research into the pathogenesis of the early "pump" failure of the ischemic heart.

Possible role of phosphate accumulation in the ischemic heart: The early "pump" failure of the ischemic heart might arise from increased cell phosphate levels that cause calcium to be sequestered in regions of the myocardial cell where this cation is unavailable to participate in excitation-contraction coupling. This hypothesis is suggested by the liberation of large amounts of inorganic phosphate in the ischemic heart that, in the absence of coronary flow, would accumulate within the cell.

Inorganic phosphate can translate a relatively small decline in high energy phosphate levels into a large signal for other metabolic responses (amplification). The following calculations of the changing concentrations of high energy phosphates in the cytosol that can follow changes in phosphocreatine levels such as have been reported in the ischemic heart utilize currently available data for the size and composition of this cytosolic compartment. These calculations are based largely on the data of Illingworth et al.[5] and on an estimated value of 2 ml of cytosolic volume per g dry weight. It is also assumed, for simplicity in these calculations, that cytosolic ADP concentration remains constant and that the relations between high energy phosphate compounds are determined by the enzymes creatine kinase and adenylate kinase as predicted from published values for the equilibrium constants of the isolated enzymes. Should any of these assumptions be incorrect, the conclusions reached would be quantitatively changed, although the results would be qualitatively the same. The initial levels of these compounds (Table I) are based on the data of Illingworth et al.[5] and have been converted to mmoles/liter cytosol.

Myocardial phosphocreatine concentration decreases rapidly in the ischemic heart, although the sum of the concentrations of phosphocreatine and creatine does not change significantly. A 75 percent fall in cytosolic phosphocreatine level, from 21.8 to 5.5 mmoles/liter, will be accompanied by a rise in cytosolic creatine level from 11.2 to 27.5 mmoles/liter (Table I). According to the equilibrium constant for creatine kinase shown in Equation 1, the initial ATP/ADP ratio in the cytosol will be approximately 200 (Table I).[5] The breakdown of phosphocreatine and the accompanying formation of creatine, as described, will, under equilibrium conditions for creatine kinase, be accompanied by a decline of cytosolic ATP from 9.7 mmoles/liter to a final level of 1.0 mmole/liter (Table I). According to the equilibrium constant for the reaction catalyzed by adenylate kinase[2,25]:

$$\frac{[ATP]\,[AMP]}{[ADP]^2} = K = 1.1 \qquad (2)$$

This change in ATP concentration will cause only a small rise in adenosine monophosphate (AMP) levels at the constant level of ADP (Table I). The net increase in total inorganic phosphate will be equal to the phosphate released from phosphocreatine plus that released from ATP (3 moles phosphate/mole ATP). The very small amount of phosphate incorporated into the increased level of AMP can be ignored. According to this calculation, the net increase in cytosolic phosphate will be more than 40 mmoles/liter. The initial level of free inorganic phosphate in the total cell is approximately 5.6 mmoles/liter cell water,[5] so that total cytosolic phosphate concentration would approach 50 mM if the anion were confined to this cellular compartment. Even if this phosphate were distributed throughout the cell, it would cause a rise of more than 20 mmoles/liter in the total cell water of areas of the ischemic myocardium in which perfusion is severely limited.

An eight-fold rise in cytosolic phosphate could have several major effects in the ischemic heart. The ability of phosphate to stimulate glycolytic flux, the main en-

ergy-producing process in the anaerobic myocardium, is well established.[4] It is also possible that the increased cell levels of phosphate could promote calcium precipitation within certain regions of the myocardium. Because the solubility product $Ca^{2+} \times HPO_4^{2-}$ is 2.4×10^{-6} (Hasselbach W, personal communication), at pH 7.0 where approximately 57 percent of the total inorganic phosphate exists as HPO_4^{2-}, a calcium phosphate precipitate will form whenever the product $Ca^{2+} \times$ Total Inorganic Phosphate exceeds 4.2×10^{-6}. Thus, if cytosolic phosphate increases to 48 mmoles/liter (Table I), a calcium-phosphate precipitate can form in any region of the myocardium in which ionized Ca^{2+} levels exceed 0.088 mmoles/liter (88 μM). Because phosphate diffuses readily across the membranes of the sarcoplasmic reticulum, which can establish Ca^{2+} concentration ratios of over 3,000 between the interior and exterior of this intracell membrane system in both skeletal[26] and cardiac (Katz AM, unpublished observations) preparations, a large rise in cellular phosphate concentration in the ischemic myocardium could trap significant amounts of calcium within the sarcoplasmic reticulum as a calcium-phosphate precipitate. In view of the well known effect of phosphate to trap calcium within the mitochondria as an insoluble calcium-phosphate precipitate,[27,28] phosphate accumulation in the ischemic heart might also cause calcium trapping within the mitochondria to decrease the availability of calcium for excitation-contraction coupling. Such changes would influence the distribution of calcium, but not its total content,[29] in areas of severe myocardial ischemia. These effects of phosphate accumulation may therefore partly explain the early "pump" failure of the ischemic heart.

The calculations presented in Table I indicate that ATP levels in the cytosol remain relatively high, even in the face of a 75 percent decrease in phosphocreatine concentration. It should be noted that the final ATP concentration of 1.0 mmole/liter remains well above that needed to saturate the substrate-binding sites of the contractile proteins and the known ion pumps (see preceding).

Summary and Conclusions

A marked reduction in oxygen tension and adenosine triphosphate (ATP) content accompanies the early "pump" failure of the ischemic heart. However, it appears to be unlikely that decreased ATP supplies for energy-consuming reactions in the myocardial cell cause the observed decrease in myocardial contractility because of the high ATP-affinity of the substrate-binding sites of known energy-consuming reactions in the heart. Furthermore, lack of chemical energy for the contractile proteins and known ion pumps would tend to promote rigor and not a decrease in contractility. Recent evidence suggests that ATP at concentrations greater than those needed to saturate the substrate-binding sites of energy-consuming reactions can exert modulatory effects on ion fluxes. These modulatory effects of ATP could allow a less severe decrease in ATP concentration to inhibit both calcium entry into the myocardial cell and calcium efflux from the sarcoplasmic reticulum. In addition, the large amounts of phosphate liberated from phosphocreatine and ATP could, by causing formation of insoluble calcium-phosphate precipitates, trap calcium in the sarcoplasmic reticulum and mitochondria in the ischemic myocardium. These proposed explanations for the early "pump" failure in the ischemic heart, together with other theories such as intracell acidosis, appear to warrant further study.

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Early Valve Replacement for Preservation of Ventricular Function?*

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"The great tragedy of science [is] the slaying of a beautiful hypothesis by an ugly fact."

T. Huxley[1]

The role of early valve replacement in the asymptomatic or minimally symptomatic patient is being discussed with increasing frequency.[2–10] This is because of the reduction in operative mortality, improvement of valve replacement devices, clarification of early long-term results (that is, 5 to 10 years) and recognition of the importance of heart failure in causing late disability and mortality.[9,11] The rationale for early operation is the prevention of deterioration of myocardial function[10] and development of irreversible heart disease[9] and, perhaps, increased long-term survival.[10] The "ugly fact" of this hypothesis may be the unpredictability of the effect of valve replacement on cardiac function and the development of serious undesirable effects (Table I), such as valve malfunction requiring reoperation, thromboembolism, loss of employment, even death.

Valve replacement is most commonly undertaken for relief of symptoms. Other indications include control of infective endocarditis, prolongation of life, relief of critical stenosis and preservation of left ventricular function. Some of these are interrelated. For example, if infective endocarditis can be controlled only with valve replacement then, obviously, surgery can prolong life. Many centers customarily relieve severe aortic stenosis (and mitral stenosis) with surgery irrespective of the patient's symptomatic state; however, even at these centers this practice is not uniform. Valve replacement may preserve ventricular function by preventing deterioration of normal or impaired function or by improving abnormal function. Successful valve replacement preserves ventricular function and prolongs life in patients with severe acute aortic and mitral regurgitation by helping to control infection or heart failure, or both. However, in most other clinical situations, the role of valve replacement in preserving ventricular function has not been clarified. Therefore, an assessment of the role of early valve replacement for the preservation of left ventricular function usually arises with relation to pure (or dominant) severe chronic aortic or mitral regurgitation, or both, an issue to which this editorial is addressed.

Risks of Valve Replacement

Before recommending early valve replacement for preservation of left ventricular function, one must evaluate the following important factors: (1) operative mortality; (2) the influence of valve replacement on left ventricular function; and (3) the proved 5 to 10 year record of valve replacement devices. The *operative mortality rate* for valve replacement varies considerably and probably averages 5 to 10 percent.[3,9,11–15] Valve replacement influences *left ventricular function* during the intra- and perioperative periods and also late after surgery. There is disagreement regarding the best

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TABLE I

Summary of a Case Illustrating Problems of Early Valve Replacement

	Before Operation	After Operation
Functional class*	?I, ?early II	Late II
Lesion	Severe aortic insufficiency	Minimal aortic insufficiency
Prosthetic orifice size	...	2.0 cm^2; 1.2 cm^2/m^2
Myocardial infarct	No	Yes (perioperative)
End-diastolic volume (ml/m^2)	215	201
Ejection fraction	0.66	0.51
Emboli	0	Cerebral, recurrent
Lactic dehydrogenase (units)	244	1200
Hematocrit (%)	38	32
Employed	Yes	No

* New York Heart Association criteria.

This 27 year old patient underwent aortic valve replacement in July 1973 and had a perioperative myocardial infarct that resulted in impaired ventricular function. He has significant hemolysis, probably a result of cloth tear. In spite of continuous adequate anticoagulation with Coumadin,® he has had documented cerebral emboli that have left him with a seizure disorder that resulted in loss of employment. It is most likely that he will need a second valve replacement.

techniques for myocardial preservation during surgery and further investigation is required.[16] The methods for assessing myocardial damage are being intensively studied but, as yet, are not fully defined. Therefore, the true incidence of the frequency and extent of perioperative myocardial damage is unknown. On the basis of electrocardiographic Q wave criteria, perioperative myocardial infarction occurs in 10 to 12 percent of patients undergoing aortic valve replacement.[17–21] Most of these infarcts occur in patients with associated coronary artery disease, but infarcts also occur in 5 percent of patients without such disease.[21] Severe myocardial damage can also occur in the absence of pathologic Q waves (Fig. 1). In such cases, myocardial infarction is presumably nontransmural but may be extensive. The late results of valve replacement on ventricular function have not been accurately defined. The experience to date is limited.[22–28] Preliminary data show that in patients who remain free of complications, an improvement in ventricular function may be common[24,27,28] after aortic valve replacement and uncommon after successful mitral valve replacement.[25] However, we have observed improvement of ventricular function after mitral valve replacement in some patients. A major problem in evaluating the effects of valve replacement on ventricular function is difficulty in separating the effects of removal of abnormal loading conditions from those of a primary change in myocardial function.

The 5 to 10 year proved record of valve replacement devices indicates that only 50 to 60 percent of patients with a ball and cage prosthesis can be expected to have no complications at the end of 5 to 7 years.[9,29,30] About 50 percent of those with a homograft valve can be expected to have no complications at 6 years.[14,31] The results with heterografts are most encouraging and may be as good as those obtained with the best mechanical prosthesis.[32–35] Heterografts have the advantage of not requiring anticoagulation therapy; however, because they are biologic valves, late failure due to valve degeneration may occur at an increased rate in the 6 to 10 years after valve replacement as has occurred with homografts. The initial results of xenograft valve replacement appear encouraging.[36,37] The long-term results of most other valve replacement devices are not yet available.[13] It is important to emphasize that some complications associated with valve replacement (for example, heart failure) relate mainly to symptomatic patients and may not be applicable to asymptomatic or minimally symptomatic patients. However, it is likely that device-related complications (for example, thromboembolism or valve degeneration) will be similar in all patient groups (Table I).

In evaluating the complications of valve replacement two points need emphasis, one relating to new devices and the other to data analysis.[38] *New devices* have often been associated with unpredicted problems. These have

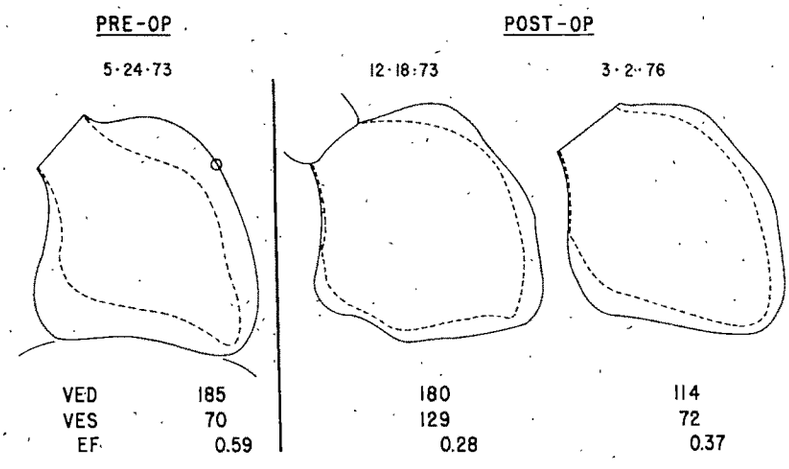


FIGURE 1. Tracings of ventriculographic silhouettes from a 54 year old man with normal preoperative coronary arteriograms who underwent mitral valve replacement in June 1973. Postoperatively he had no Q waves but widespread deep S-T depression and T wave inversion that persisted for many days. Preoperatively (PRE-OP) he was in New York Heart Association functional class III. Postoperatively (POST-OP) his functional status deteriorated to class IV and he lost his job. Three years later he is symptomatically "better" but cannot undertake much activity and continues to be totally disabled. The numbers show ventricular volumes (ml/m^2) as determined with left ventriculography. EF = ejection fraction; VED and VES = end-diastolic and end-systolic volume, respectively.

included silicone rubber ball variance, thromboembolic complications, stuck poppets with close tolerance valves, cloth tear, excessive hemolysis, obstruction of nonanticoagulated aortic prosthesis and valve malfunction and degeneration.[6,9,13,14,38–40] This list only emphasizes that introduction of a new device or a new model of an older prosthesis, even with small changes, may lead to complications that are unpredictable or do not become apparent for several years.

Actuarial techniques probably allow the most meaningful analysis of long-term results.[38,39,41] Previously, an example has been presented of 32 complications over 5 years in 400 patients. The 5 year complication rate would be only 8 percent. Because in most instances a larger number of patients will have completed 1 year than will have completed 5 years of follow-up, and the complications are cumulative, it can be shown by use of actuarial analysis that the true complication rate is not 8 percent but 1.5 percent at the end of 2 years and 60 percent (!) at 5 years.[38] Therefore, it is important that (1) the number of patients evaluated is adequate, (2) the patients are followed up for at least 5 years, and (3) the data are appropriately presented to allow assessment of the long-term complication rate.

To summarize, the present risks of valve replacement include (1) an operative mortality rate of at least 5 percent, (2) an incidence rate of perioperative myocardial damage of 10 percent or more, and (3) a 30 to 50 percent incidence rate of significant complications at the end of 5 to 6 years in operative survivors. The beneficial effects of valve replacement on ventricular function are largely unknown. After successful aortic valve replacement, left ventricular function can be expected to improve if there are no complications and if ventricular dysfunction was not too advanced before valve replacement. After successful mitral valve replacement improvement in ventricular function may be unlikely. In both instances the results are currently unpredictable.

The Problems and Their Solution

"Early" valve replacement for preservation of ventricular function is *not clinically indicated* at present because (1) techniques of myocardial preservation during surgery need refining, (2) replacement devices have to be shown to have a much lower complication rate at 5 to 10 years of follow-up, and (3) the late effects on ventricular function need to be defined.

Considerable effort is now being directed to reducing myocardial damage during surgery.[16,42–45] Meticulous care in maintaining adequate coronary perfusion, as advocated by McGoon,[46] with or without other adjunct measures may prove to be the most reliable. It is hoped that "newer" devices currently in use or others yet to be introduced will have a lower complication rate at 5 to 10 years of follow-up. The early and late effects of valve replacement on ventricular function will be systematically and prospectively studied over the next few years.

When this information is available, physicians must decide whether the results of valve replacement are superior to results without valve replacement. If they are superior, then early valve replacement will be clearly indicated; if they are not, the procedure will not be clinically indicated. At that time if we do not know whether valve replacement is better or worse than no valve replacement, then, at best, a clinical trial is indicated. It is worth reemphasizing[38] that (1) a clinical trial should be undertaken only with devices that have been used in patients for 5 or more years and that have known long-term complication rates; and (2) the cardiologist and cardiovascular surgeon have joint responsibility in such an undertaking with the patient being a fully informed partner.

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Idiopathic Hypertrophic Subaortic Stenosis Afflicted: Idols of the Cave and the Marketplace*

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Idiopathic hypertrophic subaortic stenosis (IHSS) or whatever name one currently chooses to apply—hypertrophic obstructive cardiomyopathy (HOCM), asymmetric septal hypertrophy (ASH) or muscular subaortic stenosis (MSS)—has been afflicted by a syndrome perhaps best described by the 16th century philosopher and scientist Sir Francis Bacon as the "idols of the cave and the marketplace,"[1] idols that have left many of us somewhat befuddled as to precisely what the entity idiopathic hypertrophic subaortic stenosis really is. As Bacon set down, idols of the cave are those false notions that stem from bias inherent in the individual person, "for everyone has a cave or den of his own, which refracts and discolours the light." The notions that arise from the "cave" are a product of a person's discipline, education, approach and viewpoint. The most troublesome of all, however, are the idols of the marketplace arising from "discourse among men with each other" which provide natural pitfalls where the "ill and unfit choice of words wonderfully obstruct the understanding."[1] If we examine the history of the discourse and understanding of idiopathic hypertrophic subaortic stenosis, we may see where idols have crept in. Such an examination is particularly pertinent in the light of the article by Raizner et al.[2] in this issue of the Journal on the clinical correlates of left ventricular cavity obliteration.

Historical Background

Idiopathic hypertrophic subaortic stenosis was first recognized as a separate "new" disease by an English pathologist, Teare, 20 years ago.[3] He recognized a peculiar abnormality of the septum of hearts from eight young patients who died suddenly. Not only was the septum abnormally hypertrophied, but it had bizarre histologic features. From the point of view of Teare, the morphologist, this disease was "asymmetric hypertrophy of the heart in young adults."[3] Teare's observations might have fallen the way of most anecdotes had they not been made when cardiac catheterization and cardiac surgery were emerging, for Lord Brock[4] almost simultaneously recognized a patient having a peculiar disease simulating aortic stenosis who at valve replacement had a normal aortic valve but a markedly hypertrophied septum. From his viewpoint this disease looked like idiopathic cardiomyopathy with functional obstruction.

Interest in this "new" disease with peculiar hemodynamics prompted extensive studies on both sides of the ocean.[5–9] In a few years it was more fully characterized as a rare disease, frequently familial, associated with cardiac hypertrophy, variable left ventricular outflow tract obstruction and symptoms of angina, syncope and sudden death. Its morphologic features remained as Teare explained them,[3,10,11] but it was not entirely clear that the pathologist and the hemodynamicist were always speaking of the same entity.

Perhaps the next important development in our understanding of hypertrophic cardiomyopathy came with another technologic advance in cardiology, the echocardiogram.[9,11] With the echocardiogram, Teare's view of the heart took on special importance because asymmetric hypertrophy of the heart could be detected noninvasively. Using asymmetric septal hypertrophy as a marker for hypertrophic cardiomyopathy, asymptomatic relatives of patients with this condition were studied noninvasively. This approach not only demonstrated the autosomal dominant pattern of "Teare's disease" but also pointed out that patients could have

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this peculiar abnormality of asymmetric septal hypertrophy and be free of clinical heart disease.[10] The echogram also demonstrated the systolic anterior motion of the mitral valve, which had been recognized with left ventricular angiography. And so, systolic anterior motion of the mitral valve (SAM) and asymmetric septal hypertrophy (ASH) became markers for this hereditary disorder of the heart.

The Intraventricular Pressure Gradient

Filtering into this series of important observations on this condition were several assumptions that reflected the bias of not only the investigators but also the methodology, and these biases achieved peculiar credence when they were incorporated into the names of this disorder. Experience with aortic valve stenosis naturally led to the assumption that a pressure gradient demonstrated at catheterization indicated obstruction to outflow of blood, and that this obstruction was characteristic of the "new disease." Thus, it was christened hypertrophic obstructive cardiomyopathy (HOCM) abroad, idiopathic hypertrophic subaortic stenosis (IHSS) in America and muscular subaortic stenosis (MSS) in Canada. For a number of reasons these titles, all of which contained the word stenosis, proved to be the idols of the catheterization laboratory. Almost immediately it was questionable whether true "subaortic stenosis" or "obstruction" to outflow existed.[6,13] Ross, Criley and others[13,14] demonstrated that the gradient measured in mid and late systole occurred after most of the blood was ejected, and could be due to cavity obliteration related to the hypercontractile state. Thus, the recording of a gradient did not prove the existence of outflow tract obstruction because another explanation for the gradient had been validated. It was also demonstrated that the subaortic gradient observed during cardiac catheterization was not specific for this new cardiac disease but could be reproduced in normal animals by the induction of hypercontractile cardiac states such as those occurring with inotropic stimulation or during hemorrhagic shock.[15–17] Despite such objections, the title of the catheterization laboratory took hold and spread. So firmly entrenched were the names idiopathic hypertrophic subaortic stenosis and hypertrophic obstructive cardiomyopathy that, when it became apparent that not all patients with these diagnoses had gradients at catheterization, the names were not scrapped, but amended. The corrective appendages were both cumbersome and of dubious precision: idiopathic hypertrophic subaortic stenosis with and without obstruction, hypertrophic obstructive cardiomyopathy with and without obstruction.

Is Asymmetric Septal Hypertrophy a Primary Disease?

Nevertheless, the catheterization viewpoint became less satisfying when it became evident that subaortic stenosis did not provide a unifying explanation or characterization of this disease. And so the echocardiographers took the lead with a view of idiopathic hypertrophic subaortic stenosis that neatly fused the original observations of both Teare and Brock. Systolic anterior motion of the mitral valve, the "unequivocal echocardiographic sign of outflow tract obstruction" [18] was a characteristic echocardiographic sign of idiopathic hypertrophic subaortic stenosis. But because systolic anterior motion of the mitral valve (or obstruction) was variable, the second echographic feature of this disease, asymmetric septal hypertrophy, ascended to become the new "unifying" link—all patients with hypertrophic cardiomyopathy, with or without obstruction, had asymmetric septal hypertrophy.[18,19] The latter, as originally described by Teare, and the bizarre septal histologic findings, were assumed to be virtually pathognomonic of the disease.[10,19] Although it is probably true that the less that is known about a disease state the more names are given to it,[20] the name of this many-named disease was again changed. With its new name, asymmetric septal hypertrophy became rapidly popular as a simplifying unifying title and concept. In part because of this alliance of words and name, the notion that asymmetric septal hypertrophy was pathognomonic of "idiopathic hypertrophic subaortic stenosis" took hold strongly—so strongly that when asymmetric septal hypertrophy was observed in other settings there was a tendency to claim that idiopathic hypertrophic subaortic stenosis was ubiquitous, rather than that asymmetric septal hypertrophy or systolic anterior motion of the mitral valve, or both, without idiopathic hypertrophic subaortic stenosis might be ubiquitous. In less than 20 years idiopathic hypertrophic subaortic stenosis came from oblivion to be a rare condition, and was finally transfigured into a relatively common clinical disease. Asymmetric septal hypertrophy was being reported as a coincident primary myocardial disease with all sorts of cardiac disorders from aortic stenosis to acromegaly.[21–24] The finding of the bizarre myocardial histologic features as described by Teare, or the presence of an outflow tract gradient at cardiac catheterization, in a number of diverse congenital malformations led some investigators to argue that this disease, asymmetric septal hypertrophy, is so prevalent that it frequently crops up coincidentally as a second independent cardiac disorder in congenital heart disease.[23,24]

Is Asymmetric Septal Hypertrophy Specific for Idiopathic Hypertrophic Subaortic Stenosis?

The current confusion over this disease can be attributed in part to the newer "idols" that have been taken as scientific truths. First, that asymmetric septal hypertrophy and myocardial fiber disarray are pathognomonic of this disease—so that the finding of one or the other in combination or separately implies a myocardiopathy, and a rather specific genetic one at that; the second, that hypertrophic cardiomyopathy is a single unifiable disease entity.

With regard to the first, asymmetric septal hypertrophy and myocardial fiber disarray are clearly not pathognomonic of myocardiopathy. Both features may be observed in normal subjects and in a variety of disease states far removed from this familial disease de-

scribed by Teare.[11,25,26] Echocardiographic and morphologic studies have shown that the normal human fetus and some newborns have asymmetric septal hypertrophy; patients with severe right ventricular hypertrophy may have asymmetric septal hypertrophy, even normal weightlifters may have it.[25–29] It is not specific for idiopathic hypertrophic subaortic stenosis. Myocardial fiber disarray is present to some extent in normal hearts and in exaggerated form in a variety of cardiac malformations.[11,25,26]

Is Hypertrophic Cardiomyopathy a Single Disease Entity?

The second idol that has taken hold in the marketplace is that hypertrophic cardiomyopathy is a single unifiable disease entity.[18,23,24] Increasingly it is becoming apparent that there are hypercontractile states that may be idiopathic, that are clinically and angiographically identical to idiopathic hypertrophic subaortic stenosis as Lord Brock saw it but are not necessarily the disease originally seen by Teare.[2,30–33] There is now evidence that the spectrum of hypertrophic cardiomyopathy is broader and more heterogeneous than we have suspected. The study by Raizner et al.[2] in the current issue of the Journal is one such example. These investigators studied a group of patients that have "functional obstruction of the left ventricle," as described by Brock, but the causes were multiple. Some appear to fall into the category of idiopathic hypertrophic subaortic stenosis with asymmetric septal hypertrophy, but many clearly do not. These are not new observations, however, just ones that we have lost sight of over the years. In 1960, Goodwin, Teare and others noted: "Thus it is clear that this syndrome of pseudoaortic stenosis is likely to be associated with more than one cause of left ventricular hypertrophy, and that the anatomical features too may be varied." [8]

Perhaps the simplest approach to hypertrophic cardiomyopathy would be to recognize its complexity. It is likely a spectrum of disease states of diverse etiology. Teare's disease may represent a familial form associated with asymmetric hypertrophy and abnormal septal histology. But cases of nonfamilial symmetrical hypertrophic cardiomyopathy also appear to exist as real entities, as do secondary hypercontractile states that may behave like primary hypertrophic disease.

When a "new" disease arrives on the scene, especially one whose characterization is dependent on new methodology, we understandably become blind men (or women) "seeing" the elephant. Bacon cautioned us against the "idols" that arise from deductions made on limited insight, which are especially misleading when they are translated into words or labels that "force and overrule the understanding, and throw all into confusion, and lead men away into numberless empty controversies and idle fancies."[1] Perhaps we should avoid the "overruling" labels of idiopathic hypertrophic subaortic stenosis, hypertrophic obstructive cardiomyopathy, and asymmetric septal hypertrophy and revert to something more precise like Brock's disease or Teare's disease until we understand more.

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President's Page

HEART HOUSE Learning Center—Dedication And Operation



Dr. Mason

Welcome to HEART HOUSE! Culminating more than a decade of sustained and cooperative planning, our HEART HOUSE Learning Center has become the operational reality we have all anxiously anticipated. Formal HEART HOUSE dedication ceremonies commemorating this major milestone in our College's development are set for October 3, 1977. It is indeed appropriate that our initial Learning Center program in cardiovascular continuing education is to be conducted by the master cardiovascular teacher, Dr. W. Proctor Harvey, on "The Bedside Art and Science of Cardiac Diagnosis" from October 19 to 21, 1977.

A brief review of the principal evolutionary events establishing HEART HOUSE is in order. In February 1968 the Board of Trustees endorsed the HEART HOUSE concept advocated by Dr. E. Grey Dimond and authorized purchase of land in the Bethesda area for the future building site. In the summer of the same year, the College purchased the ideally located 10 acre tract of land at 9111 Old Georgetown Road for $500,000. After considerable soul searching by those officers concerned about the College assuming such a debt, the contract was signed by the College president, Dr. George E. Burch, "under the clock" in the Biltmore Hotel in New York City. The 19 member HEART HOUSE Committee was then formed in the spring of 1969 with Dr. B. L. Martz, serving as chairman-in-chief, Drs. Dwight E. Harken, Dr. Samuel M. Fox, III and Dr. Dimond, serving, respectively, as chairmen of Subcommittes on Campaign Funding, Building and Facilities and Curriculum Development.

In the summer of 1972 the HEART HOUSE Development Office was formed within the College's administration headquarters in Bethesda. In November 1972 the architectural firm of Perkins and Will was selected and in June 1973 a College Conference on Educational Technology was held in Kansas City, Missouri. In July 1973 Theodore G. Kummer joined the College as staff director of our fund raising campaign and coordinator with the architect and audiovisual consultants. Thanks to the vigorous efforts of a constellation of Fellows and friends of the College, particularly the indefatigable Dr. Harken aided by Dr. Donald A. Dupler (Foundation Division chairman), Dr. Kenneth G. Kohlstaedt (Pharmaceutical Division chairman), Dr. Henry D. McIntosh (Membership Division chairman), Mr. Kummer and our executive director, Mr. William D. Nelligan, funds for HEART HOUSE reached the $1 million mark in October 1973, passed $2 million in May 1974, crossed $3 million in October 1975 and are now above the $4 million level. With the construction contract signed in September 1975, the memorable HEART HOUSE groundbreaking ceremonies took place on September 29, 1975. Construction phases proceeded on schedule and by May 1977 it was possible for the College staff to move into our new building.

Concurrently with these impressive facility developments, the College officers recognized the need to recruit an outstanding staff of professional educators to implement the goals of our Learning Center. Fortunately, the College was able to attract an extremely capable director for continuing education, Robert K. Richards, PhD, from his directorship of continuing education at the University of Michigan Medical School. Dr. Richards then appointed to his College Learning Center staff, James K. Walker, MA, director of educational programs and Dennis B. Webster, MA, director of educational resources. The HEART HOUSE Learning Center receives overall guidance from the College's seven member Learning Center Committee chaired by Dr. Suzanne B. Knoebel. The goals for HEART HOUSE established by the Learning Center Committee include developing programs in accordance with the individual educational needs of attending physicians, encouraging continuous and systematic learning, utilizing the most efficient educational methods and extending the effectiveness of continuing medical education by educational research.

The Learning Center and its goals and objectives represent the ultimate successful results of the College's long-standing commitment to excellence in continuing cardiovascular education. Competent physicians have always recognized educational activities as an integral part of their professional life. This commendable self discipline coupled with the increased emphasis on continuing education as a result of requirements for recertification and renewal of licensure makes the thoughtful creation of the HEART HOUSE Learning Center most timely. The philosophy and facilities for the Learning Center programs are designed for individualized and small group instruction and for exploring contributions that educational technology can make to more effective continuing education. For example, the innovative manikin "Harvey" developed by Dr. Michael S. Gordon, as well as a specially designed learner-response system will be used by both individuals and groups. Even the HEART

HOUSE grounds are to be park-like in appearance to provide an atmosphere conducive to learning outside the building. Furthermore, the Learning Center will develop Outreach Programs to provide educational materials for home study.

At present, 20 programs are scheduled during the Learning Center's first year of operation. Each program utilizes a modern classroom equipped with 67 chairs specially designed for cardiovascular learning. Each of these swivel chairs has a four-channel video display, a stethophone and a learner-to-instructor electronic response system. Six adjacent Conference Rooms provide opportunity for smaller interactive sessions, and individual study is afforded within the Griffith Resource Library. In addition, it is planned that HEART HOUSE will be the center for future Bethesda Conferences at the College.

The Griffith Resource Library deserves special consideration. This facility is designed to serve several important purposes. Compilation of a core cardiovascular library of books, journals, films, video-cassettes, slide tapes and audiocassettes is being guided by the Library Acquisitions Committee chaired by Dr. Martz. Further, the Griffith Library will be closely coordinated with the resources of the nearby National Library of Medicine, including a terminal for on-line interface with the Medline systems. In addition, this Resource Library contains six individual study rooms equipped with a variety of audiovisual aids to learning.

Our Learning Center is a prudent investment in the progress and future success of the College, as well as in advancing the state of the art in continuing medical education. The close proximity of HEART HOUSE to cooperating health facilities such as The National Institutes of Health, National Library of Medicine, Armed Forces Institute of Pathology, six University Medical Schools, U.S. Naval Medical Center, Walter Reed Army Medical Center and to the nation's capital which will enhance its educational dividends. Our new HEART HOUSE Learning Center promises to be the finest continuing education facility in the world. Now is the time that we enjoy the fruits of our labors and for each of us to participate in its many educational opportunities.

Dean T. Mason, MD, FACC
President
American College of Cardiology

NEW MEMBERS

The following individuals were elected to membership in the American College of Cardiology on May 11, 1977 in the category indicated.

FELLOWSHIP

ANTONATOS, Panagiotis G., MD, Athens, Greece
ASSAD-Morell, Jose L., MD, Monterrey, Mexico
BALASUBRAMANIAN, V., MD, New Delhi, India
BERENS, Stephen C., MD, Encino, CA
BOONE, John A., MD, Vancouver, Canada
CAMARA, Augusto A., MD, Rizal, Philippines
CAUDILL, Darrell R., MD, Atlanta, GA
CLAPS, Albina A., MD, Staten Island, NY
DUVOISIN, George E., MD, Spokane, WA
EWART, James A., MD, Walnut Creek, CA
FERNANDEZ, Javier, MD, Browns Mills, NJ
FLEMING, William H., MD, Omaha, NE
FORDTRAN, Robert L., III, MD, Corpus Christi, TX
GARCIA, Otto L., MD, Miami, FL
GIBSON, Robert C., MD, Portland, OR
GOULD, Kenneth L., MD, Seattle, WA
GREENE, Harry L., MD, Baltimore, MD
GREGORY, Jonathan M., MD, Traverse City, MI
GROVER, D. N., MD, Pune, India
GUSS, Stephen B., MD, Morristown, NJ
HALLEY, M. Martin, MD, Topeka, KS
HARDESTY, Robert L., MD, Pittsburgh, PA
HENKEL, Terry W., MD, Louisville, KY
HENRY, Philip D., MD, St. Louis, MO
JOLLY, Walter W., MD, Indianapolis, IN
JUK, Steven S., Jr., MD, Columbia, SC
KIM, Youn S., MD, Grand Rapids, MI
KINAHAN, Patrick J., MD, Vancouver, Canada
KRAKOFF, Lawrence R., MD, New York, NY
KUBLER, Wolfgang, MD, Heidelberg, Germany
LEE, Myles E., MD, Beverly Hills, CA
MACKENZIE, James W., MD, Piscataway, NJ
MILLER, Stephen W., MD, Boston, MA
NARENDRAN, C. S., MD, Leavenworth, KS
OKIES, J. Edward, MD, Portland, OR
PITT, Bertram, MD, Baltimore, MD
RABOW, Fred I., MD, Montreal, Quebec, Canada
RICHARDS, Kent L., MD, Albuquerque, NM
ROSENSWEIG, Jacob, MD, Memphis, TN
SALOP, Arnold, MD, Ossining, NY
SANKARAN, A., MD, Madras, India
SATIN, Lawrence Z., MD, Riverdale, MD
SCHEIB, Ronald J., MD, Miami Beach, FL
SHAY, Thanad S., MD, Peoria, IL
SINGH, Bramah N., MD, Los Angeles, CA
SPOTO, Edward, Jr., MD, Tampa, FL
SRINIVASAN, Nathapet V., MD, Fullerton, CA
STORZ, Siegfried O., MD, Ventura, CA
THOMPSON, Peter L., MD, Medlands, Australia
TRACY, Gerald P., MD, Scranton, PA
WANG, Hsien C., MD, Richmond Heights, OH
WARE, George W., MD, Silver Spring, MD
WEINBERG, Paul M., MD, Natick, MA
WINKLE, Roger A., MD, Palo Alto, CA
WISE, Daniel E., MD, Gainesville, FL
ZACHARIAS, Anoar, MD, Toledo, OH
ZARREN, Harvey S., MD, Marblehead, MA

ADVANCE TO FELLOWSHIP

ADROUNY, Zaven A., MD, Burlingame, CA
AHMED, Syed A., MBBS, Danville, VA
DAVIS, Michael A., MD, Sacramento, CA
FONG, Bernard W. D., MD, Honolulu, Hawaii
GELLES, Jeremiah M., MD, Brooklyn, NY
LEVI, George A., MD, Worcester, MA
McGINN, Francis X., MD, Upper Montclair, NJ
MOOTHART, Richard W., MD, Colorado Springs, CO
PRICE, Herman L., MD, San Rafael, CA
RITCHIE, Keith L., MD, Salt Lake City, UT

ASSOCIATE FELLOWSHIP

ALTHOUSE, Lemuel B., Jr., MD, Camp Hill, PA
AYERDI, Evalt, MD, Ft. Leonard Wood, MO
COVITZ, Wesley, MD, Augusta, GA
GELBER, Philip, MD, Jamaica, NY
GROSSMAN, Joseph A., MD, New York, NY
MANCINI, James R., MD, Attleboro, MA
MARTIN, M. Herbert, Jr., MD, Gainesville, FL
OWLIA, Dariush, MD, Hartford, CT
PIZZARELLO, Roy A., MD, Manhasset, NY
ROSENCRANS, Ernest, MD, Iowa City, IA
SAITO, Satoshi, MD, Tokyo, Japan
SEHAPAYAK, Georgina K., MD, Fort Worth, TX
SOLON, Thomas J., MD, Chestertown, MD
STETLER, William R., MD, Birmingham, AL

STORER, William R., MD, Indianapolis, IN
VASEENON, Thamnium, MD, Kansas City, KS

ADVANCE TO ASSOCIATE FELLOWSHIP

BIALOW, Martin R., MD, Largo, FL
FLORES, Milagros C., MD, Dearborn, MI

AFFILIATE

DANG, Collin R., MD, Honolulu, Hawaii
ESGRO, Philip J., MD, Springfield, PA
HUSSAIN, Karim M., MD, Emeryville, CA
JONES, Harry D., MD, Reno, NV
JUGDUTT, Bodh I., MB, ChB, Baltimore, MD
PARK, Chang S., MD, Girard, OH
RUFFY, Rodolphe, MD, Indianapolis, IN
SOLY, Kristine L., MD, Philadelphia, PA
STUART, Robert J., Jr., MD, Long Beach, CA

AFFILIATES (In Cardiovascular Related Training) who have been inducted into the College since January 1, 1977

AHMADPOUR, Hedayatolah, MD, South Pasadena, CA
BALAMOHAN, Ramalingam, MD, West Orange, NJ
BASKERVILLE, Archer L., MD, Iowa City, IA
BEUTEL, Ernest W., MD, Chicago, IL
BHATIA, Harmohinder S., MB, BS, East Orange, NJ
CHANDURKAR, Sudhakar N., MD, East Cleveland, OH
CHAUDRY, Khalid R., MB, BS, Upper Darby, PA
CHENG, Chao-Tang, MD, Parma, OH
CHI, Tao-Nan, MD, Norwalk, CT
COLLINS-NAKAI, Ruth L., MD, Edmonton, Alberta, Canada
EBERZ, Dennis A., MD, Pittsburgh, PA
ELKAYAM, Uri, MD, New York, NY
GEISER, Edward A., MD, Glenshaw, PA
GLASSER, Jack D., MD, Providence, RI
GOTTWIK, Martin G., MD, Newton, MA
GRACE, R. Randall, MD, Houston, TX
HASHEMIAN, Mahmoud, MD, Toledo, OH
HAUSER, Andrew M., MD, Ann Arbor, MI
HEIBIG, Jacques, MD, San Francisco, CA
HOEKENGA, David E., MD, Albuquerque, NM
HOFFMANN, Robert M., MD, South Burlington, VT
JAIN, Suresh Chand, MD, Mexico, DF, Mexico
JOYE, James A., MD, Sacramento, CA
JUAREZ-URIBE, Joel, MD, Stone Mountain, GA
KAIMAL, Parameswara K., MD, Cleveland, OH
LEE, Jung Hun, MD, Euclid, OH
MARY-RABINE, Luc J. MD, New York, NY
MILLER, Mark P., MD, Sacramento, CA
MONOSON, Peter A., MD, San Antonio, TX
MOODY, Joe M., Jr., MD, San Antonio, TX
MORRISON, Douglass A., MD, Tampa, FL
MOTAMEDI, Mohamad R., MD, Pittsburgh, PA
MOTTA, Jorge A., MD, Palo Alto, CA
MSUMBA, Cameron A., MD, Shrewsbury, MA
OH, Keun Chang, MD, Brooklyn, NY
OKONKWO, Charles I., MD, Staten Island, NY
OLIVER, David C., MD, Winston-Salem, NC
PAMATMAT, Adelfo N., MD, Detroit, MI
PEZZELLA, Stephen M., MD, Worcester, MA
PRABHU, H. Sudhakar, MD, Brooklyn, NY
QARAMAN, Abdulwahab L., MD, Elizabeth, NJ
RIZVI, Syed M. N., MB, BS, Hasbrouck Heights, NJ
RUDIN, Barry R., MD, Paramus, NJ
SANDOR, George G. S., MB, ChB, Toronto, Ontario, Canada
SCHROEDER, David P., MD, Columbus, OH
SHERMAN, Frederic M., MD, New York, NY
SICHERMAN, Harlan Jay, MD, Philadelphia, PA
SIDELL, Peter M., MD, Rochester, MN
SUDARSHAN, Sriram, MD, Elizabeth, NJ
TOBEY, Martin A., MD, Dallas, TX
UY, Santos A., Jr., MD, Euclid, OH
WARD, David E., MB, BS, London, England
WHITE, David H., MD, San Antonio, TX

CHANGE IN THE TRAINING REQUIREMENTS FOR THE AMERICAN BOARD OF INTERNAL MEDICINE'S SUBSPECIALTY EXAMINATIONS

The American Board of Internal Medicine has announced a significant change in policy regarding its training requirements. This change will affect physicians desiring admission to a subspecialty examination who began their residency training in *internal medicine* before June 1, 1970. At present, these physicians are considered to have met the training requirements for admission to a subspecialty examination after completing one year of acceptable training in the subspecialty. If once informed of admission to a subspecialty examination, these physicians *will continue* to be considered to have fulfilled the Board's training requirements in that subspecialty. Beginning with the subspecialty examination offered in 1981, however, *all physicians* not previously admitted to an examination will be required to meet the same training requirements which apply to physicians beginning their residency training after June 1, 1970. These requirements currently involved two full years of acceptable training in the subspecialty. A complete description of the Board's policies and procedures may be obtained by directing a written request to: American Board of Internal Medicine, 3930 Chestnut Street, Philadelphia, PA 19104. The next examination in Cardiovascular Disease will be offered in June 1979.

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists, educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Borys Surawicz, MD, FACC, Chairman
National Program Committee

Programs and faculty are subject to change. For further information write Mary Anne McInerny, Director, Extramural Programs Department, Division of Continuing Education, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

SEPTEMBER THROUGH DECEMBER 1977

1977

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director. Pacific Medical Center, San Francisco, CA

SEPT. 7–10 — **Core Curriculum: Interpretation and Therapy of Cardiac Arrhythmias.** Leonard S. Dreifus, FACC and Yoshio Watanabe, FACC, directors. Philadelphia Marriott Motor Hotel, Philadelphia, PA

SEPT. 29–30 — **Cardiac Electrophysiology for a Cardiologist.** Borys Surawicz, FACC and Leonard S. Gettes, FACC, directors. Continental Inn, Lexington, KY

OCT. 3–5 — **Advanced Echocardiography.** Harvey Feigenbaum, FACC, director and Betty C. Corya, James C. Dillon, FACC and Arthur E. Weyman, FACC, co-directors. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 6–8 — **New Diagnostic and Therapeutic Approaches in Cardiology—1977.** Edmund H. Sonnenblick, FACC and James E. Scheuer, FACC, co-directors. The Plaza, New York, NY

OCT. 10–13 — **Electrocardiography: Core Curriculum and Self-Assessment.** Paul L. McHenry, FACC, director and Charles Fisch, FACC, co-director. Indianapolis Hilton Hotel, Indianapolis, IN

OCT. 11–14 — **Electrocardiography: Core Curriculum and Self-Assessment.** Arthur Selzer, FACC, director. Golden Gateway Holiday Inn, San Francisco, CA

OCT. 13–15 — **New Techniques and Concepts in Cardiology: Pathogenesis and Treatment of Coronary Artery Disease; Sudden Death Without Coronary Disease.** Stephen E. Epstein, FACC, director. The Washington Hilton Hotel, Washington, DC

OCT. 13–15 — **The Clinical Spectrum of Adult Heart Disease.** Jonathan Abrams, FACC, director and Paul T. Cochran, FACC, co-director. University of New Mexico School of Medicine, Basic Medical Sciences Building, Albuquerque, NM

OCT. 21–23 — **Practical Cardiology—1977.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt Hotel, Monterey, CA

NOV. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, co-directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

NOV. 8–10 — **Clinical Perspectives in Valvular and Ischemic Heart Disease.** James T. Mazzara, FACC, director and Richard J. Kennedy, FACC, co-director. St. Vincent's Hospital and Medical Center of New York, New York, NY

NOV. 20–23 — **Coronary, Valvular and Myocardial Heart Diseases: Structure-Function Correlations and Implications for Therapy.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg, VA

DEC. 2–4 — **Advances in Heart Disease—1978.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 9–11 — **Tenth Annual Cardiovascular Symposium: Theory and Practice of Cardiology Today.** Henry I. Russek, FACC, director. Americana Hotel, New York, NY

LEARNING CENTER: PROGRAM CALENDAR

Dear Colleague:

You are invited to participate in one of the initial programs to be held in the College's new HEART HOUSE Learning Center.

Throughout the construction and staffing of the Learning Center our purpose has been to provide the resources necessary to attain a new standard of excellence in cardiovascular continuing education. Now that we are operational, our focus is directed toward you—our program participant. Our intent is to develop and conduct these programs in a way which will support your commitment to learning and enhance your efforts to provide quality patient care. Topics for our 1977–78 Learning Center Programs have been chosen to meet the needs of physicians from many different specialties who care for patients with cardiovascular problems. Our Program Directors are recognized for their teaching talent and their commitment to cardiovascular education. Our innovative staff of educators and the superb Learning Center facility are ready. Now, all we need is you.

We hope to see you at the Learning Center this year.

Best personal regards,
SUZANNE B. KNOEBEL, M.D., F.A.C.C.
Chairman, Learning Center Committee

For additional information contact Mary Ann Henry, Program Coordinator, Learning Center Programs, ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014. (301) 897-5400.

OCTOBER THROUGH DECEMBER 1977

Oct. 19–21 and Nov. 16–18 **The Bedside Art & Science of Cardiac Diagnosis: Clinical & Physiological Correlation.** W. Proctor Harvey, MD, FACC, & Antonio C. de Leon, MD, FACC, directors.

Nov. 1–3 **Clinical Decision Making in Coronary Artery Disease.** Arthur Selzer, MD, FACC, director.

Nov. 9–10 **Pacemaker Therapy: Specific Needs for Optimal Patient Benefits.** Leonard S. Dreifus, MD, FACC, director.

Nov. 21–23 **Diagnosis and Management of Clinically Important Arrhythmias.** William P. Nelson, MD, FACC, director.

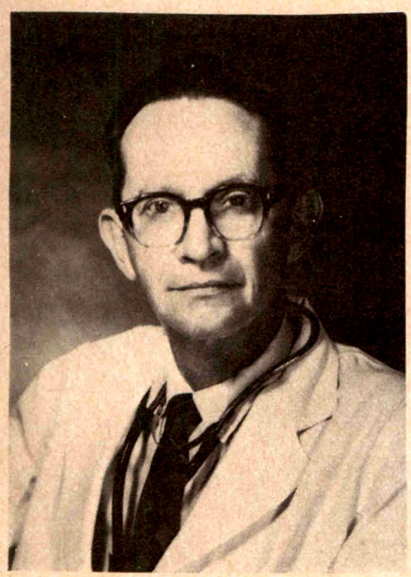
27th ANNUAL SCIENTIFIC SESSION
AMERICAN COLLEGE OF CARDIOLOGY

Anaheim, California **March 6–9, 1978**

- **Abstracts**
  Entries must be postmarked no later than September 19, 1977
- **Technical Exhibits**
  Deadline for requests for space: October 17, 1977
- **Scientific Exhibits**
  Deadline for requests for space: October 17, 1977
- **Young Investigators' Awards Competition**
  Entries must be postmarked no later than November 1, 1977

For application forms, write Patrick A. Ziarnik, Director, Annual Scientific Session Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

WILLIAM J. GRACE, MD, FACC
1916–1977



Dr. William J. Grace, editor of *The American Journal of Medicine* and a widely respected cardiologist, was host, year after year, to the College's continuing education program in myocardial infarction and coronary care at St. Vincent's Hospital in New York, a course that was regularly oversubscribed. This program was based on the first coronary care unit established in the metropolitan New York area. Dr. Grace was a man of many talents, an able administrator, a great teacher, lecturer and editor and, above all, a compassionate and dedicated physician who trained numerous interns and residents in a pattern of superb patient care. The record of his life is a recital of activity on important boards and committees, educational assignments, editorial work and, for our College, a real interest in forwarding our function of spreading cardiologic knowledge.

Bill was born in St. Joseph, Missouri, on March 18, 1916. He received his Bachelor of Science degree from St. Peter's College in Jersey City, New Jersey in 1938 and his MD from Cornell University in 1942. He interned at Roosevelt Hospital in New York City and came back to Cornell as resident in internal medicine in the New York Hospital.

He was admitted as a Fellow in our College in 1951 and was immediately active in College affairs. He served as College governor for downstate New York from 1962 to 1965; he was on the Continuing Education Committee from 1970 to 1973 and a member of the Board of Trustees from 1970 to 1974. He was our representative on three committees of the American Heart Association: Clinical Cardiology, Coronary Care and Critical Care Medicine. He was our program representative in the American Medical Association's Section of Cardiovascular Disease from 1973 to 1977.

Bill had Fellowships in the College of Chest Physicians, College of Physicians and College of Clinical Pharmacology, and the New York Academy of Medicine. In each organization he was not content to relax as one of the Fellows. He served on committees; he was a member of the Board of Trustees of the New York Academy of Medicine and of the New York Heart Association.

Bill's bibliography began in 1948 and included more than 150 papers. He held editorial appointments on six journals and from July 1973 until his death served as editor of the prestigious *American Journal of Medicine*. At the same time he was Director of Medicine in St. Vincent's Hospital in New York and made daily teaching rounds. He died on February 18, 1977 at the age of 60 years.

Bill Grace will be remembered for his kindness and for his sincere dedication to the members of his staff; the interns that he trained will be a living memorial to a distinguished Fellow of our College.

Philip Reichert, MD, FACC
Historian
American College of Cardiology

INSTRUCTIONS FOR AUTHORS

The editors of THE AMERICAN JOURNAL OF CARDIOLOGY welcome concise articles devoted to cardiovascular disease. Articles must be contributed solely to THE AMERICAN JOURNAL OF CARDIOLOGY and become the property of the Publisher. The Publisher reserves copyright and renewal on all published material, and such material may not be reproduced in any form without the written permission of the Publisher. Statements in articles are the responsibility of the authors. Authors will assist the editors in the prompt processing of manuscripts if these instructions are followed:

THE WHOLE PAPER

- Address manuscript to Managing Editor, American Journal of Cardiology, 666 Fifth Ave., New York, NY 10019.
- Submit two copies of all elements of the article: text, references, legends, tables and figures.
- Arrange the paper in this order: (1) title page; (2) abstract; (3) text; (4) references; (5) legends; (6) tables; and (7) figures.
- Number all pages in above sequence, beginning with title page as 1, abstract as 2, etc.
- Type all matter: (1) on 8½ × 11 opaque white bond paper; (2) in duplicate; (3) on one side of each sheet only; (4) double-space; (5) leave wide margins, all four sides.

THE TITLE PAGE

- Include first names, degrees and, where applicable, FACC for all authors.
- Provide a short running title of 3 to 6 words.
- Insert at bottom: name and address of institution from which work originated plus information about grants.
- Add at bottom the phrase "Address for reprints: . . ." followed by full name and address with zip code.

THE ABSTRACT

- Limit words as follows: 100 to 250 words for major articles; 50 to 100 words for case reports.
- Add at end of abstract: list of 2 to 6 key words and subjects for indexing.

THE TEXT

- Type in duplicate; double-space.
- Do not use abbreviations such as SVC, WPW: write out; superior vena cava, Wolff-Parkinson-White.
- Abbreviate measurements (mm, kcal and the like) as recommended in the Style Manual for Biological Journals, American Institute of Biological Sciences, 3900 Wisconsin Avenue, N.W., Washington, D. C.
- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
- Place acknowledgments at end of text, before references.

THE REFERENCES

- Type in duplicate; double-space.
- Number the references in order in which they are mentioned in text.
- Provide concluding page numbers for all journal references and specific page numbers for all book references. Indicate all abstracts by the abbreviation (abstr).
- Follow the general arrangement, abbreviations and punctuation styles shown below.

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- Start at top of new page.
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- Identify at the end of each legend and in alphabetical order all abbreviations in the figure described.

THE TABLES

- Start each table at top of new page.
- Type in duplicate; double-space.
- Give each table a number (in roman numerals; Table I, II, etc.) and a title. Number the tables in order in which they are mentioned in the text.
- Provide a footnote to each table—identifying **in alphabetical order** all abbreviations used.

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- Submit 2 glossy prints (not originals) of each photo and drawing.
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- Use black ink for all charts (line drawings). Make decimals, broken lines, etc. strong enough for reproduction.
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For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

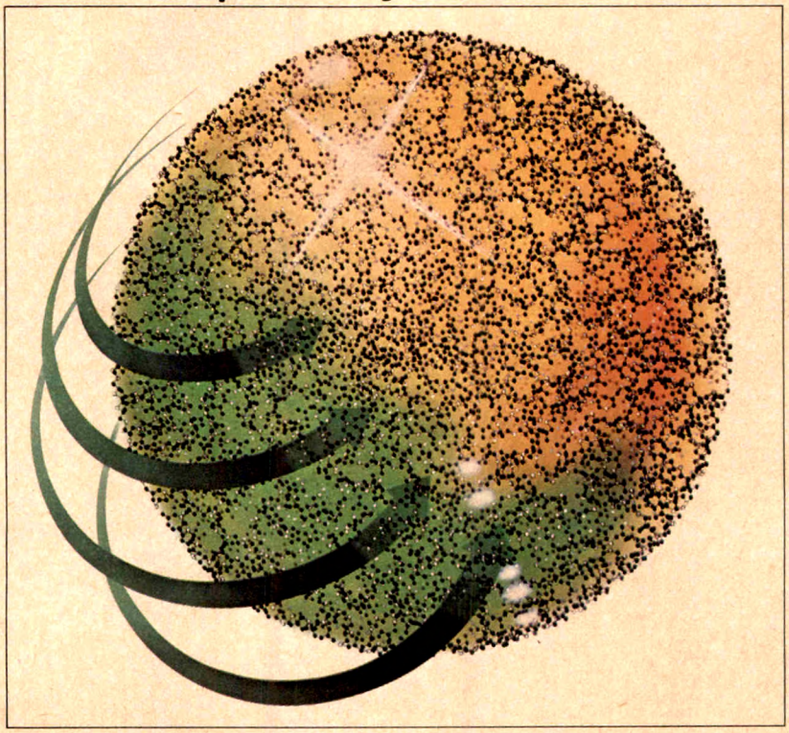
(Author: all book references should have specific page numbers)

Upjohn

introduces

new Colestid®

colestipol hydrochloride



Adjunctive to diet

lowers plasma cholesterol through nonsystemic action

A89

Upjohn

new Colestid®

colestipol hydrochloride

Adjunctive to diet lowers serum cholesterol through a nonsystemic action

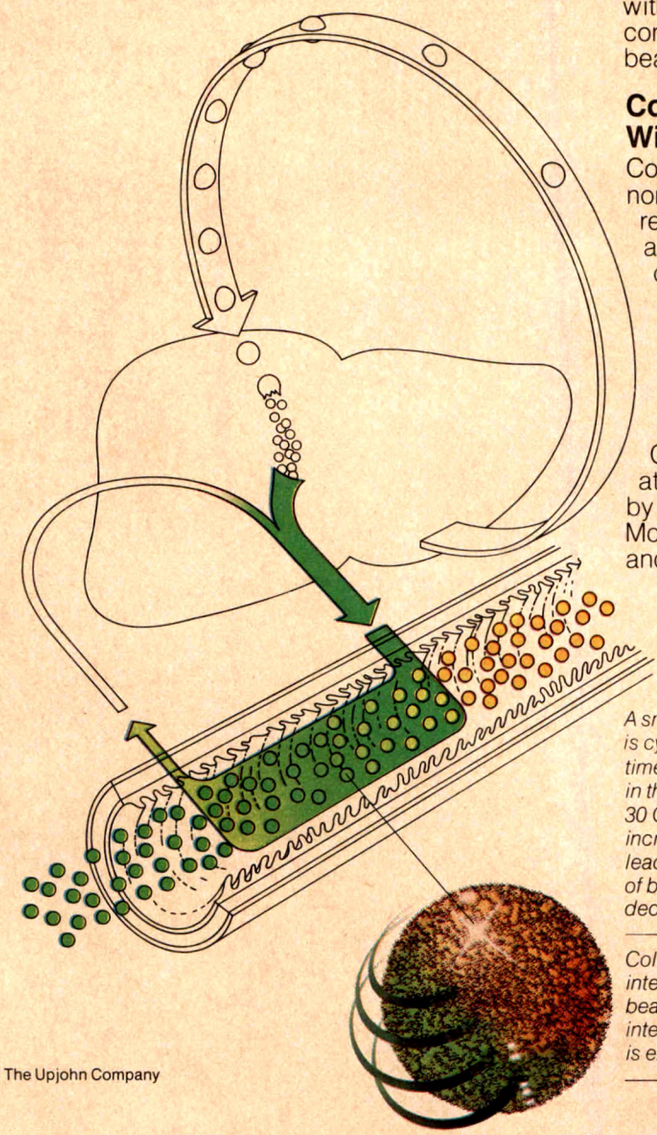
- for primary hypercholesterolemia
- effective long-term adjunct to diet
- nonsystemic mode of action
- offers convenient b.i.d. dosage

Colestid is a high-molecular-weight, anion-exchange copolymer. It consists of virtually insoluble macromolecular beads, each containing approximately 10^{15} potential bile-acid-binding sites within its mesh structure. The average 5 Gm dose contains an estimated 1,250,000 macromolecular beads.

Colestid Acts Only Within the Lumen of the GI Tract

Colestid, a bile sequestrant, is virtually nonabsorbed. Most bile acids are normally reabsorbed; however, the partial removal of a small amount of bile acids from the enterohepatic circulation by Colestid increases hepatic production of bile acids from cholesterol. This results in a decrease in the cholesterol-rich, low-density lipoproteins and thus a decrease in serum cholesterol.

The most common adverse reactions to Colestid are confined to the gastrointestinal tract. Constipation is the major single complaint, and at times is severe and occasionally accompanied by fecal impaction. Hemorrhoids may be aggravated. Most instances of constipation are mild, transient, and controlled with standard treatment.



A small pool of bile acids, about 2 to 4 Gm, is cycled through the intestine several times daily, and only about 0.6 Gm is lost in the feces. With Colestid therapy (15 to 30 Gm/day), the bile salt excretion is increased about 2 to 2½ times. This leads to increased hepatic production of bile acids from cholesterol, thereby decreasing serum cholesterol levels.

Colestid acts within the gastrointestinal tract. Its macromolecular beads bind bile acids in the intestine and form a complex that is excreted in the feces.

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Scope of Colestid Clinical Studies

One hundred and forty-four investigators and over 2,500 patients treated with Colestid (colestipol hydrochloride) participated in clinical trials of this new bile-sequestering agent. Thirty clinical studies helped to determine the efficacy, safety, and tolerance of Colestid in lowering serum cholesterol.

Colestid Therapy Guidelines

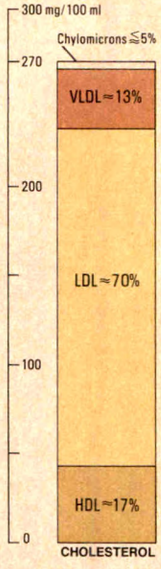
Colestid is indicated as adjunctive therapy to diet in the management of patients with elevated serum cholesterol due to primary hypercholesterolemia (elevated low-density lipoproteins).

The beta-lipoprotein (or low-density lipoprotein) transports most of the serum cholesterol, and it is believed that the fall in serum cholesterol with Colestid therapy is secondary to an increased clearance of the cholesterol-rich, low-density lipoprotein.

The reduction of serum cholesterol levels is usually evident within one month. When Colestid is discontinued, cholesterol levels usually return to baseline levels within one month.

Colestid has been shown to have no effect on, or to increase, triglyceride levels. Failure of cholesterol to fall or a significant rise in the triglyceride level should be considered as indication to discontinue Colestid.

Approximate contribution of the four lipoproteins to total serum cholesterol in a normal subject, fasting state.



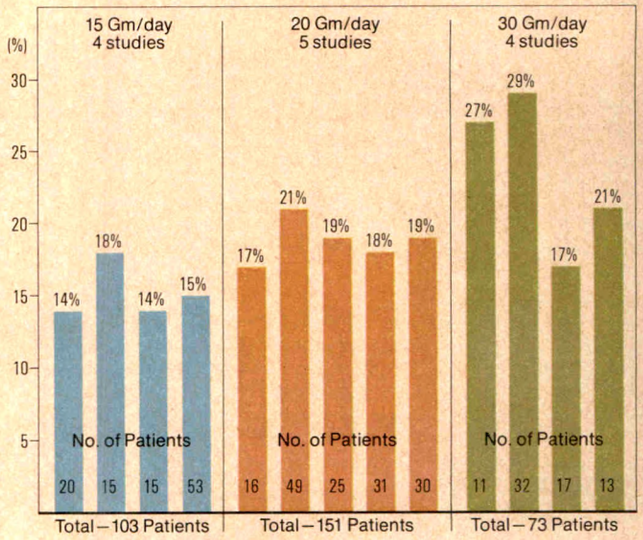
It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Investigations now in progress may yield an answer to this question.

Colestid Offers b.i.d. Convenience

Colestid 10 Gm twice a day is usually effective and avoids the obstacle of midday dosage. In general, however, Colestid dosage may be adjusted to meet the cholesterol-lowering requirements of the individual patient. For adults, the recommended dosage range is 15 to 30 Gm per day, divided into two, three, or four doses. To avoid accidental inhalation or esophageal distress, Colestid should not be taken in its dry form.

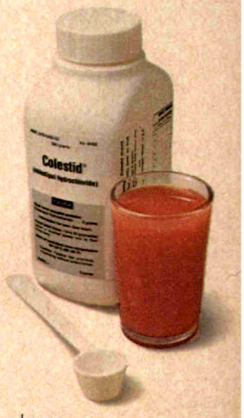
Measure of Colestid Efficacy

Average Cholesterol Reduction at 15, 20, and 30 Gm daily



Colestid is recommended in doses of 15 to 30 Gm per day, administered in divided doses, two, three, or four times daily.

Easy and Versatile Administration



The small particle size and neutral taste of Colestid (colestipol hydrochloride) make it a readily acceptable adjunct to your patient's diet. For example, it may be taken conveniently with orange juice in the morning and with applesauce at night. Colestid mixes easily with almost any liquid or pulpy fruit (such as milk, water, fruit juices, carbonated beverages, pineapple, applesauce, cereals, and soups).

Colestid is available in measured-dose packets of 5 Gm (30 to a carton) or in bottles of 500 Gm (with calibrated measuring spoon).

Drug Interactions

Patients should take other drugs at least one hour before or four hours after Colestid to minimize possible interference with their absorption.

Discontinuing Colestid could pose a hazard to health if a potentially toxic drug that is significantly bound to Colestid has been titrated to a maintenance level during Colestid therapy. Particular caution should be observed in digitalized patients, since there are conflicting results for the effect of Colestid on the absorption of digoxin and digitoxin.

For a summary of prescribing information, please see last page of this advertisement.▶

Upjohn

new Colestid®
colestipol hydrochloride

Lowers plasma cholesterol through a nonsystemic action adjunctive to diet

INDICATIONS AND USAGE Since no drug is innocuous, strict attention should be paid to the indications and contraindications, particularly when selecting drugs for chronic long-term use.

Colestid (colestipol hydrochloride) is indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low-density lipoproteins). It has been shown that Colestid has no effect on, or may increase, triglyceride levels.

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on morbidity or mortality due to atherosclerosis, including coronary heart disease. Investigations now in progress may yield an answer to this question.

CONTRAINDICATIONS Colestid (colestipol hydrochloride) is contraindicated in individuals with hypersensitivity to any of its components.

WARNINGS TO AVOID ACCIDENTAL INHALATION OR ESOPHAGEAL DISTRESS, COLESTID SHOULD NOT BE TAKEN IN ITS DRY FORM. ALWAYS MIX COLESTID WITH WATER OR OTHER FLUIDS BEFORE INGESTING.

PRECAUTIONS Before therapy with Colestid, a vigorous attempt should be made to control serum cholesterol with diet and weight reduction; any underlying disorder should be treated.

Colestid may interfere with normal absorption and fat, vitamins A, D, and K. Supplemental vitamins A and D should be considered.

Colestid may be associated with hypoprothrombinemia from vitamin K deficiency and can be prevented by administration of vitamin K1.

Serum cholesterol and triglyceride levels should be monitored. Colestid may raise the serum triglycerides in long-term use and, in some patients, the cholesterol levels return to baseline or rise above baseline.

Colestid may produce or severely worsen preexisting constipation. Dosage should be decreased in these patients, since impaction may occur. Particular effort should be made to avoid constipation in patients with symptomatic coronary artery disease. Constipation associated with Colestid may aggravate hemorrhoids.

Use in Pregnancy and Childhood The use of Colestid in pregnancy or lactation or by women of childbearing age requires that the potential benefits of drug therapy be weighed against the possible hazards to the mother and child. The safe use of Colestid resin by pregnant women has not been established. Safety and effectiveness in children have not been established.

DRUG INTERACTIONS Colestid may have a strong affinity for anions other than the bile acids. Colestid may delay or reduce the absorption of concomitant oral medication. The interval between the administration of Colestid and any other medication should be as long as possible. Patients should take other drugs at least one hour before or four hours after Colestid.

In vitro Colestid binds a number of drugs. *In vivo* studies disclosed significant effects on drug availability for L-thyroxin and aspirin, and possibly for warfarin and nicotinic acid. Decreased serum tetracycline levels were observed in a clinical study.

In preliminary studies, drug availability did not appear to be significantly altered for phenobarbital, cortisone acetate, chlorpromazine, sulfadiazine, clofibrate, and hydrochlorothiazide. Particular caution should be observed with digitalis preparations, since there are conflicting results for the effect of Colestid on the availability of digoxin and digitoxin. Discontinuing Colestid could pose a hazard to health if a potentially toxic drug that is significantly bound to the resin has been titrated to a maintenance level while the patient was taking Colestid.

ADVERSE REACTIONS

1. Gastrointestinal The most common adverse reactions are gastrointestinal. Constipation, one patient in 10, is the major single complaint and at times is severe and occasionally accompanied by fecal impaction. Hemorrhoids may be aggravated. Some patients require decreased dosage or discontinuation of therapy. About one in 30 to one in 100 patients reported abdominal discomfort (abdominal pain and distention), belching, flatulence, nausea, vomiting, and diarrhea. Peptic ulceration, gastrointestinal irritation and bleeding, cholecystitis, and cholelithiasis have been reported by fewer than one in 500 patients and are not necessarily drug related.

2. Hypersensitivity Urticaria and dermatitis were noted in fewer than one in 1,000 patients. Asthma and wheezing were not reported in the Colestid studies but have been noted during treatment with other cholesterol-lowering agents.

3. Musculoskeletal Muscle and joint pains and arthritis have had a reported incidence of less than one in 1,000 patients.

4. Neurologic Headache and dizziness were noted in about one in 300 patients; anxiety, vertigo, and drowsiness were reported in fewer than one in 1,000.

5. Miscellaneous Anorexia, fatigue, weakness, and shortness of breath have been seen in 1 to 3 patients in 1,000. Transient and modest elevations of serum glutamic oxaloacetic transaminase and of alkaline phosphatase were observed in various patients treated with Colestid. Some patients had increased serum phosphorus and chloride with decreased sodium and potassium.

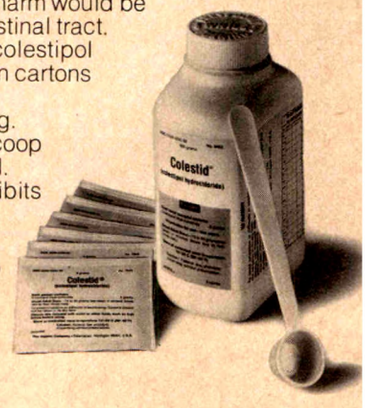
OVERDOSE Overdosage of Colestid (colestipol hydrochloride) has not been reported. Should overdosage occur, however, the chief potential harm would be obstruction of the gastrointestinal tract.

HOW SUPPLIED Colestid (colestipol hydrochloride) is available in cartons of 30 packets and in bottles containing 500 grams of drug. Each packet or each level scoop supplies 5 grams of Colestid.

Caution: Federal law prohibits dispensing without prescription.

For additional information, see your Upjohn representative or consult package circular.

MED-1



Upjohn The Upjohn Company, Kalamazoo, Michigan 49001, U.S.A.

J-4815-6

July 1977

Others may look similar...

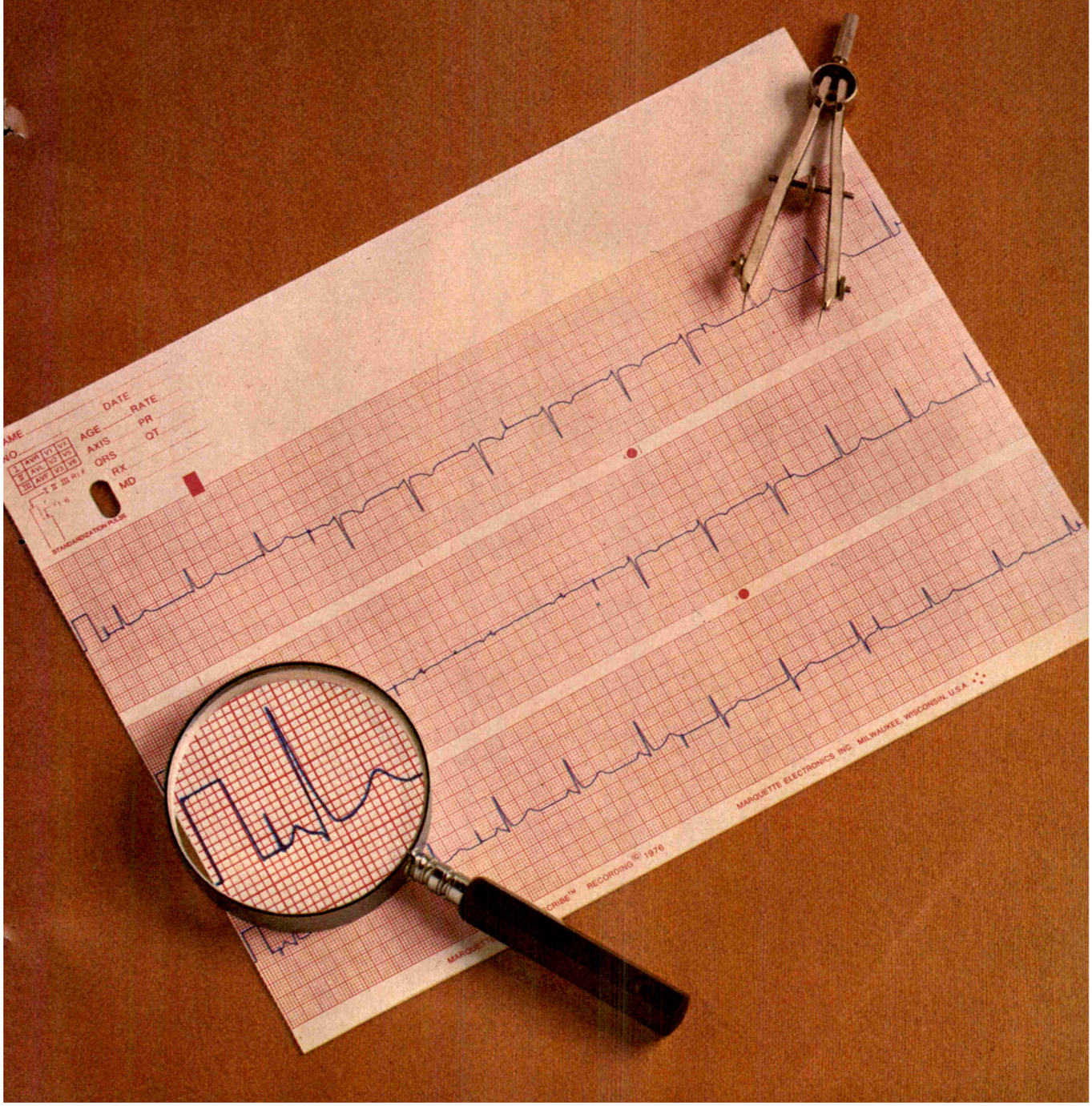
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Three channel ECG's at their finest ... from the innovator of automatic Electrocardiographs.

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American
Pacemaker

8100 SERIES A-V SEQUENTIAL DEMAND PACEMAKER LITHIUM POWERED

APC's 8100 Series pacer is an R-wave inhibited A-V sequential pacemaker primarily indicated for use in patients with sick sinus syndrome, sinus bradycardia or sinoatrial block; particularly if complicated by heart failure, low cardiac output syndrome or atrio-ventricular block.

The power source of the pacer is a hermetically sealed battery pack containing four series/parallel connected lithium-silver chromate cells for power supply redundancy. The functional characteristics of lithium cells make them ideally suited for use in implantable devices where long term, reliable operation is highly desirable.

The 8100 Series pacer reflects, as do all APC pacemakers, the application of conservative technology in the manufacture of implantable devices of the highest quality and reliability.

FEATURES

- Hermetically sealed electronics and power source for maximum reliability.
- Exceptional resistance to EMI (electro-magnetic interference).
- Provides for ready determination of battery performance in the absence of patient history.
- Smaller size, lighter weight for greater patient comfort.
- Full two year warranty and a theoretical service life greater than four years.
- Redundantly connected lithium cells for added safety.
- Standard bipolar connections.
- Early warning of end of life.
- Technical consultation or pacer delivery available 24 hours a day. Dial 617 AM-PACER.

SPECIFICATIONS

Factory Preset Rates: 71 BPM with 225 msec A-V interval, Model 8175-A
80 BPM with 250 msec A-V interval, Model 8175-B
80 BPM with 175 msec A-V interval, Model 8175-C
92 BPM with 150 msec A-V interval, Model 8175-D

Pulse Width: 0.9 - 1.0 msec

Output: Typical; into 500 ohm load
Ventricular: 5.4 volts peak
Atrial: 5.2 volts peak

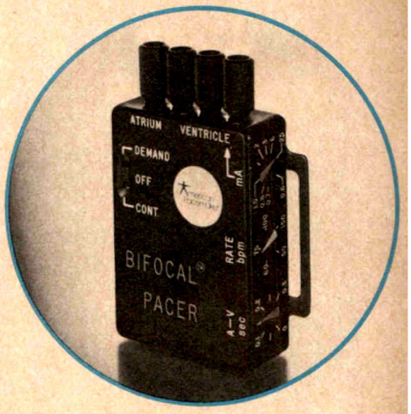
Sensitivity: 1.7 mV typical

Refractory Period: 220 msec following pacer pulse
140 msec following R-wave

Weight: 150 grams

Volume: 80 cc

Power Source: Four SAFT Li210 cells series/parallel connected - hermetically sealed

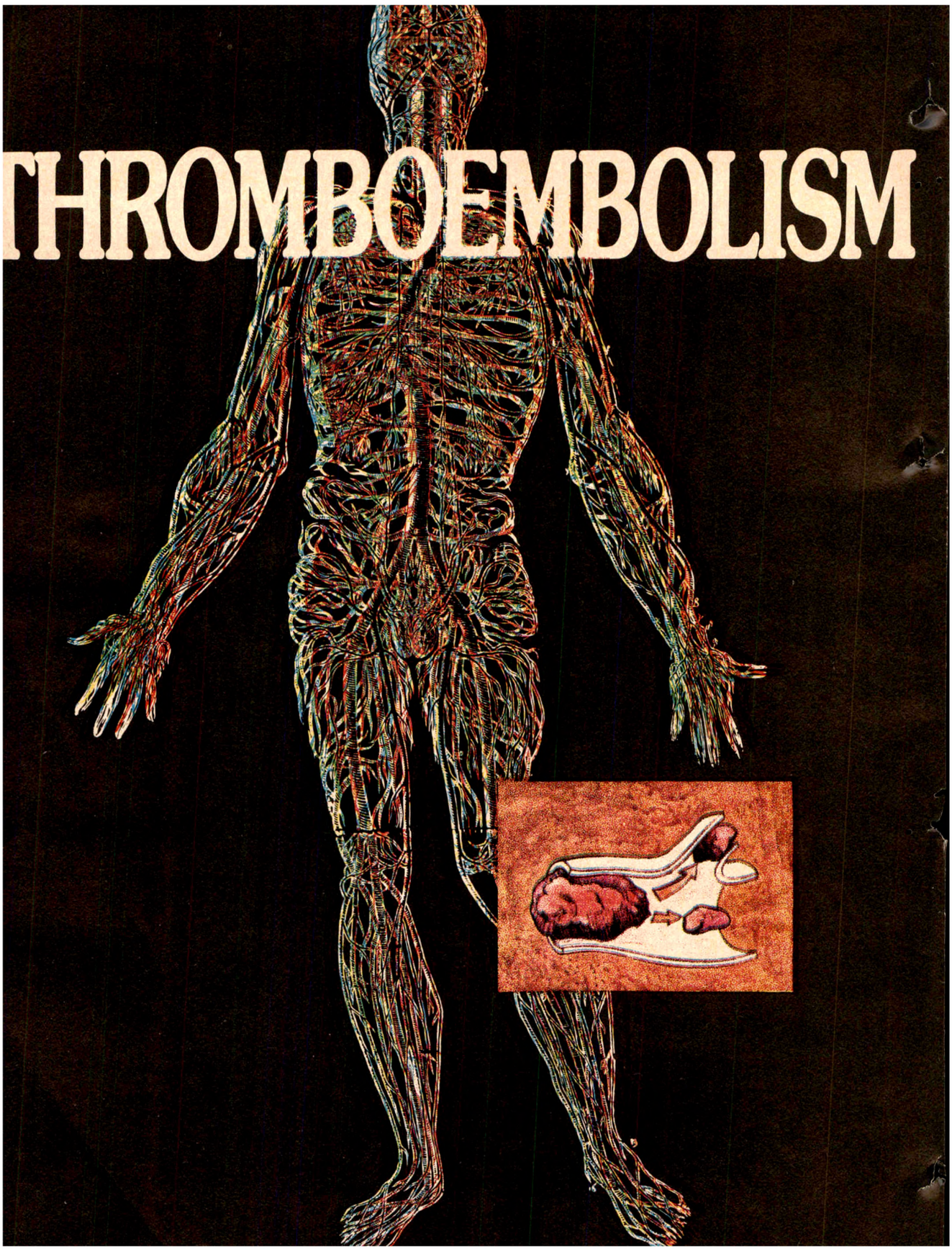


Model 2020
Extracorporeal
BIFOCAL® Pacemaker

American Pacemaker
CORPORATION

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THROMBOEMBOLISM



COUMADIN® (CRYSTALLINE SODIUM WARFARIN U.S.P.)

FOR ORAL ANTICOAGULATION

Prophylactic Use

A number of cardiac syndromes can predispose patients to thromboembolic episodes. The greatest threat of thromboembolism, however, exists in patients with a history of obesity, excessive cigarette smoking or previous episodes of venous thrombosis or pulmonary embolism. Postoperative patients requiring extended immobilization and the elderly are at high thromboembolic risk as are the severely injured—particularly those over 40 years with fractures of the hip, pelvis or lower extremities—and patients undergoing elective cup arthroplasty or pelvic surgery.

Emphasis should be placed on prophylaxis for those patients predisposed to thromboembolism. The oral anticoagulant of choice is COUMADIN® (crystalline sodium warfarin U.S.P.)

Therapeutic Use

For established thromboembolism, administration of I.V. heparin followed by oral anticoagulant therapy is a cornerstone of treatment. COUMADIN,® a chemically pure oral anticoagulant with high predictability of response, is a mainstay of effective therapy.

Dosage and Administration

In patients receiving COUMADIN,® prothrombin time should be maintained at 1.5 to 2.5 times the control until results stabilize. Dosage and administration should be individualized according to prothrombin time results and reevaluated periodically throughout therapy.

Patients should be well informed about their condition and medication, since factors such as dietary change, travel, other medication, change in physical condition and abrupt environmental change may influence prothrombin time and, therefore, response to COUMADIN.®

The oral anticoagulant of choice COUMADIN®

(CRYSTALLINE SODIUM WARFARIN U.S.P.)

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

Before prescribing, please see prescribing information on following page.

COUMADIN® is an Endo registered U.S. trademark;
U.S. Pat. No. 3,077,481 (Reissue No. 25,866)

COUMADIN®

(CRYSTALLINE SODIUM WARFARIN*)

DESCRIPTION COUMADIN® (crystalline sodium warfarin), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of sodium warfarin virtually eliminates trace impurities present in amorphous sodium warfarin, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN® (crystalline sodium warfarin) is therapeutically equivalent to amorphous sodium warfarin.

ACTIONS COUMADIN® and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN® usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences–National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN® is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN® (crystalline sodium warfarin) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1) central nervous system; (2) eye; (3) traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1) gastrointestinal, genitourinary or respiratory tracts; (2) cerebrovascular hemorrhage; (3) aneurysms–cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** polyarthritis, vitamin C deficiency, major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Sodium warfarin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN® are given together, a period of 4 to 5 hours should elapse after the last intravenous dose and 12 to 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when sodium warfarin is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:
Lactation–coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Prolonged dietary deficiency** (cachexia, vitamin K). **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**–sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, menometrorrhagia, allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN®, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN*.

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders–infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency–steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cinchophen; clofibrate; COUMADIN® overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN® underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN®. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN® (crystalline sodium warfarin) include:

1. Minor or major hemorrhage from any tissue or organ–which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and an extremely rare reaction consisting of hemorrhagic infarction and necrosis of the skin.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN* patient aids are available to physicians on request.

The administration and dosage of COUMADIN® must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN® should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic prothrombinopenia are 1½ to 2½ times the normal prothrombin time (e.g. 21 to 35 seconds, with a control of 14 seconds).

Induction–40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Maintenance–Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy–The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery–The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN® be adjusted to maintain the prothrombin time at approximately 1½ to 2 times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN* with Heparin–Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in situations of great emergency to administer sodium heparin initially along with COUMADIN®. The initial dose of heparin and injectable COUMADIN* may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN*, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, and preferably 4 to 5 hours after the last intravenous injection or 12 to 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN® (crystalline sodium warfarin), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN* may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN® administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can be obtained.

SUPPLIED Tablets: COUMADIN® (crystalline sodium warfarin). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white, 25 mg red. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous sodium warfarin lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution. 50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

*Present as crystalline sodium warfarin isopropanol clathrate.

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DUPONT

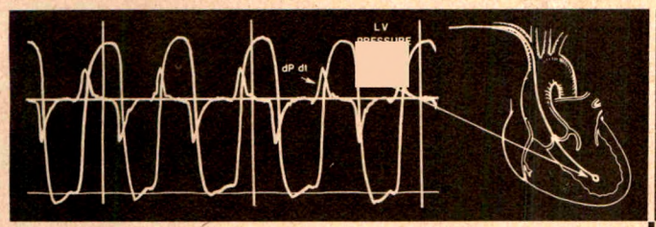
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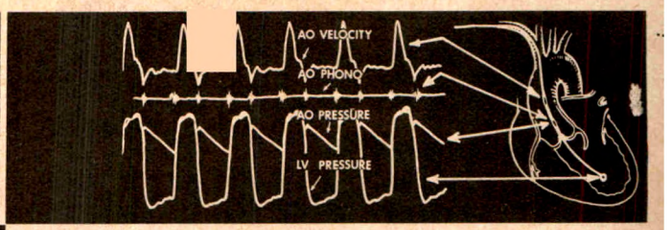
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EDO-046C

March, 1977

MILLAR TRANSDUCERS





Catheter Pressure Transducer

TO RECORD
- PRESSURE AT SOURCE
- TRUE WAVEFORMS
- PHONOCARDIOGRAMS

PRESSURE SENSOR FEATURES
- THERMAL STABILITY
- EXCELLENT LINEARITY
- HIGH NATURAL FREQUENCY

Millar MIKRO-TIP® Catheter Pressure Transducers are available in a variety of configurations. Catheter French sizes are from 4F to 8F. One, two or three pressure sensors may be spaced along a single catheter, some with lumen for blood sampling or with lumen for high speed injection.

Catheter Velocity/ Pressure Transducer

TO RECORD
- FLUID VELOCITY
- PRESSURE AT SOURCE
- PHONOCARDIOGRAMS

VELOCITY SENSOR FEATURES
- LINEAR STABLE OUTPUT
- LOW POWER DISSIPATION
- BIDIRECTIONAL MEASUREMENT

Millar MIKRO-TIP® Catheter Velocity/Pressure Transducers are available in a variety of configurations. Catheter French sizes are from 6F to 8F. One electromagnetic fluid-velocity sensor and one or two pressure sensors may be spaced along a single catheter. In the size 8F catheter only, a pressure sensor may be placed at the same location as the fluid-velocity sensor.

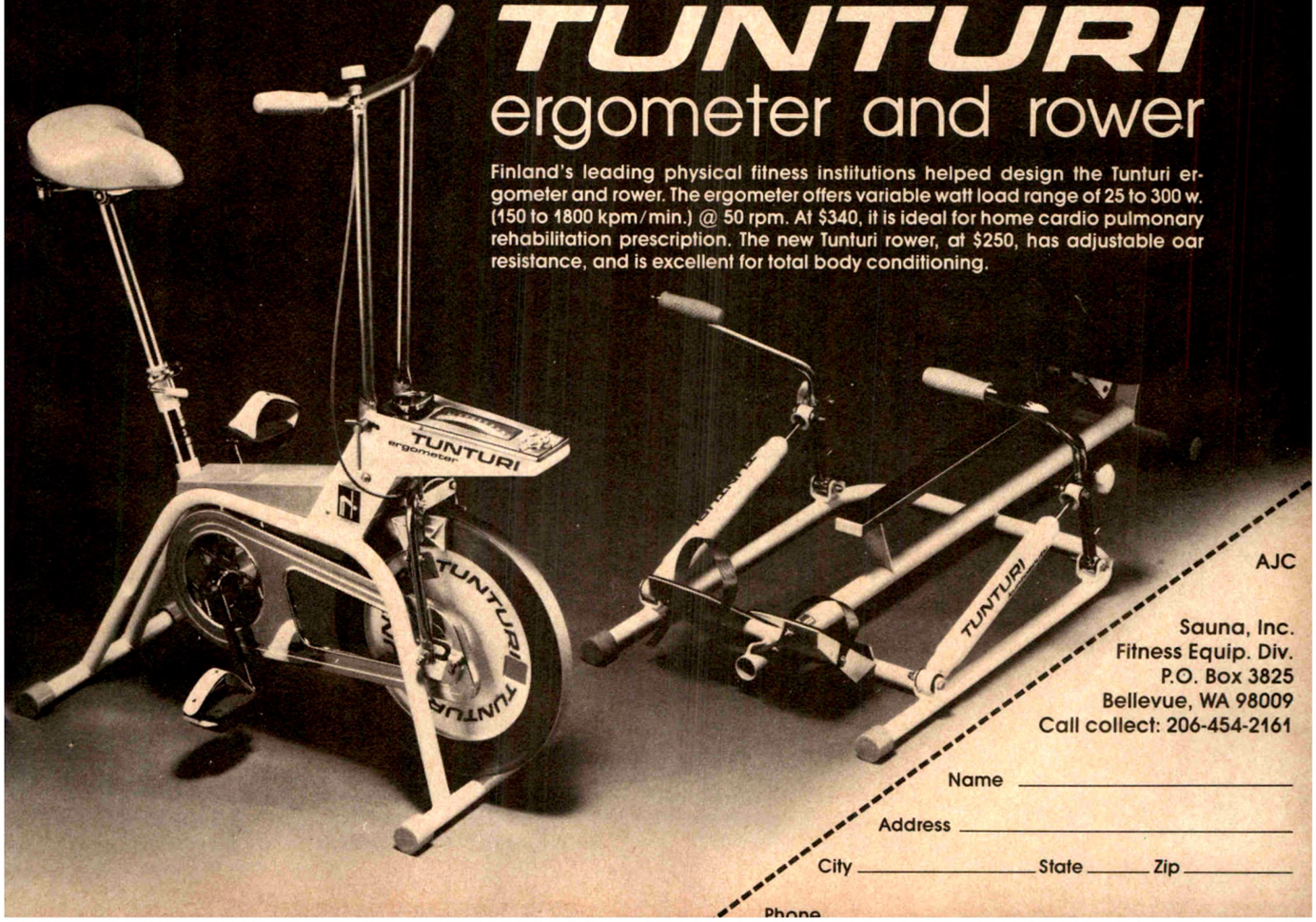
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Finland's leading physical fitness institutions helped design the Tunturi ergometer and rower. The ergometer offers variable watt load range of 25 to 300 w. (150 to 1800 kpm/min.) @ 50 rpm. At $340, it is ideal for home cardio pulmonary rehabilitation prescription. The new Tunturi rower, at $250, has adjustable oar resistance, and is excellent for total body conditioning.



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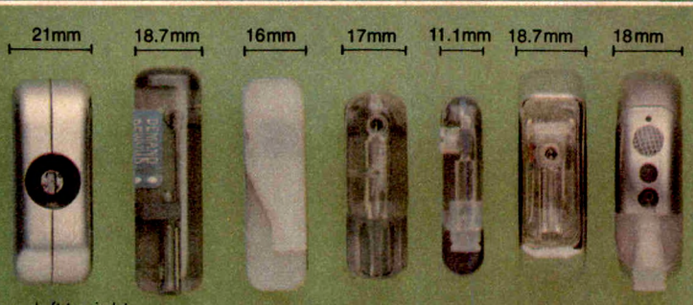
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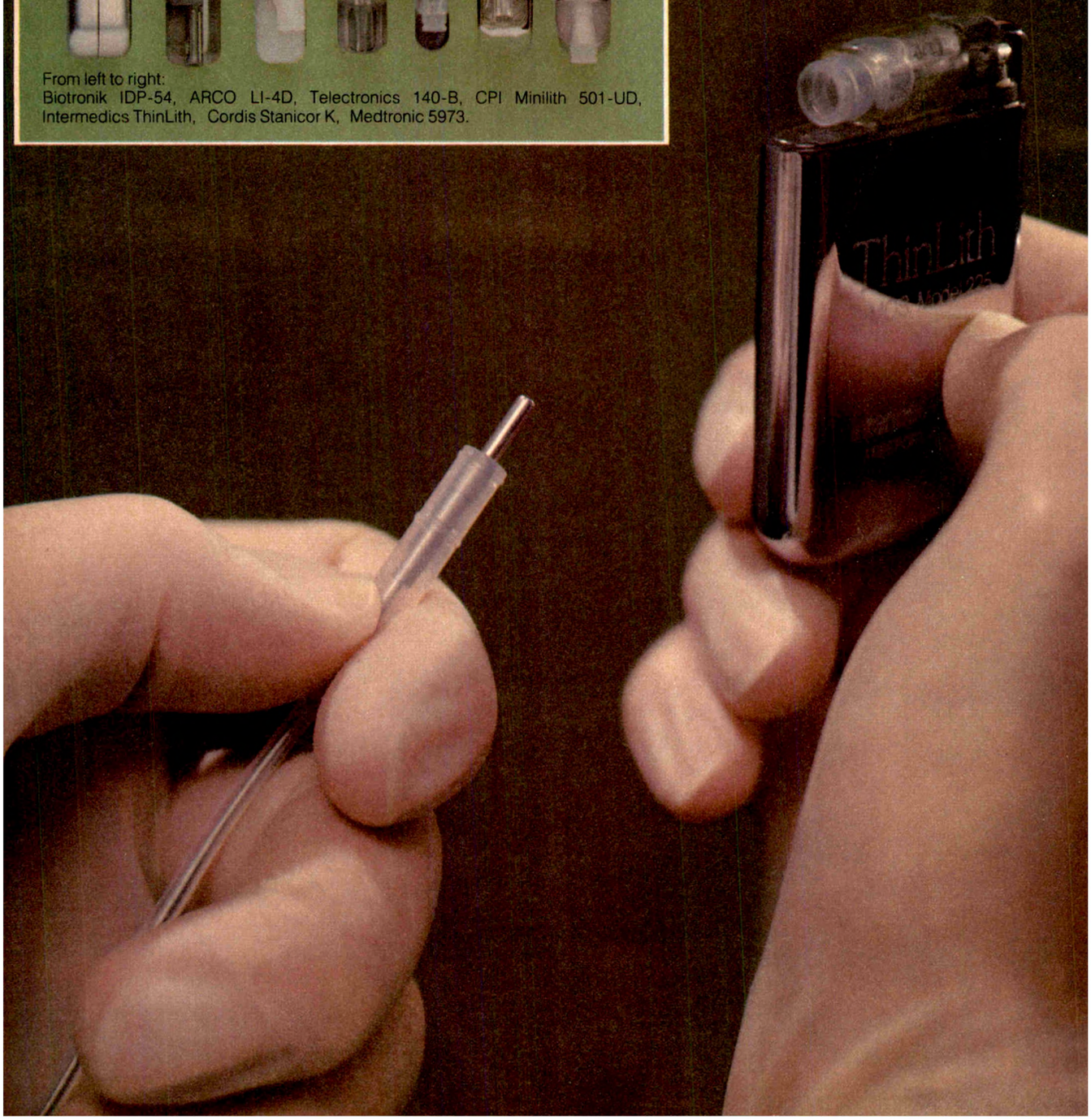
Phone

ThinLith™

Today's thinnest lithium pacemaker.



From left to right:
Biotronik IDP-54, ARCO LI-4D, Telectronics 140-B, CPI Minilith 501-UD, Intermedics ThinLith, Cordis Stanicor K, Medtronic 5973.



Part of a total superior system from Intermedics, Inc.

Intermedics now offers the *thinnest* lithium cardiac pulse generators available today — the ThinLith Model 225 and Model 227. The unipolar ThinLith,



which measures only 11.1 mm in thickness, virtually eliminates the skin bulge common with thicker pulse generators, adds to patient comfort and greatly reduces skin pressure necrosis. In addition, the ThinLith's light weight and smoothly-rounded corners reduce the chance of migration within the body.

The ThinLith employs the same dependable c-mos circuitry which has proven successful in other Intermedics pulse generators. This double ion diffusion c-mos circuitry provides optimum sensing and stimulation performance, even at low voltage levels. To aid in the creation of the ThinLith, we have greatly reduced the number of components and miniaturized the electronics by using a hybird circuit which employs advanced technology in microelectronics.

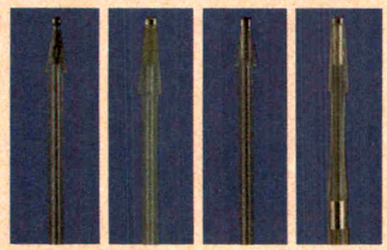
As a power source, Intermedics' engineers chose the highly reliable Catalyst Research, single cell, lithium-iodine battery, proven in testing and in human use for five years. The ThinLith Model 225 is powered by a Catalyst Research 803-30 lithium battery. The ThinLith Model 227 is powered by a Catalyst Research 803-23 lithium battery. The two models are identical except for battery capacity and the volume and mass differences caused by the variation in battery size. These power sources have a theoretical longevity of ten and eight years, respectively, and are backed by an Intermedics' replacement credit agreement.

After assembly and testing, the circuitry and power source are hermetically sealed in electromagnetic interference resistant, 316L stainless steel and sterilized for implant. The ThinLith, as are all Intermedics pulse generators, is designed to accept all of the more commonly used leads without need for an adapter.

The predecessors to the Intermedics ThinLith are the unipolar C-MOS I mercury-zinc pulse generator and the C-MOS I Lithium, and the InterLith™ generators in unipolar and bipolar models. These have been the choice of pacemaker implants around the world.

Life-Prolonging Leads

As part of their life support system, Intermedics manufactures a quality line of high density platinum-tipped leads which provide low pacing and sensing thresholds, thereby increasing the longevity of the pulse generator. Materials for lead manufacture were carefully selected for their chemical and functional compatibility as well as their strength and flexibility. Closed coil construction resists dislodgement and prevents lead fractures and provides lead flexibility so important to the physician. Intermedics' leads are available in 2 choices of flexibility and a variety of tip configurations: unipolar spherical, conical and blunt-tip; and bi-polar blunt-tip.



Trans-Telephonic Monitoring Systems At No Additional Charge

Intermedics is the only pacemaker manufacturer in the market today which provides the patient with a trans-telephonic monitoring service — Trace-A-Pace™ * — absolutely free of charge to the patient, physician, hospital, or health carrier. At the request of the physician, the patient receives a light-weight and easy-to-use (requires no electrode wires) transmitter. Then, at intervals determined by the physician, the patient simply dials our toll-free number and has a rhythm strip and digital interval rate count recorded. In all cases, the physician receives a full report and copy of the rhythm strip by mail. However, should an irregularity be observed, the



physician is notified immediately by telephone. This service greatly reduces the time required for patient follow-up and increases the patient's confidence and mobility.

24-Hour Service

All Intermedics' representatives are on call 24 hours a day. When necessary, they can have an Intermedics implantable device in your hands shortly after you call.

For the location of your nearest Intermedics representative, or for additional information about our products, call toll-free 1-800-231-2330. In Texas, call collect 1-713-233-8611.

Intermedics Inc.
P.O. Box 617 • Freeport, Texas 77541

KayCiel®
(potassium chloride)
vs.
Diet



ORANGE FLAVORED

KayCiel® Elixir		KayCiel® Powder	
Each 15 ml (20 mEq of potassium chloride) contains:		Each *Solodose®* packet (20 mEq of potassium chloride) contains:	
Calories	17	Calories	0
Sodium	0 mg	Sodium	0 mg

CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.
WARNING: Do not use excessively.
PRECAUTIONS: Administer with caution and adjust to the requirements of the individual patient. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.
Patients should be cautioned to adhere to dilution instructions.
ADVERSE REACTIONS: Potassium intoxication indicated by listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac depression, arrhythmias, arrest and heart block. Vomiting, nausea, abdominal discomfort and diarrhea may occur.
OVERDOSAGE: In case of excessive use resulting in hyperkalemia or potassium intoxication, discontinue potassium chloride administration or take other steps to lower serum levels if indicated.

Cooper Compliance Tip

Help assure that your older patients take medications properly by printing your instructions in large letters. You might also send a copy of the instructions to the patient's spouse. Please forward your compliance tip to Cooper Laboratories, 300 Fairfield Road, Wayne, N.J. 07470, Att: W.F. Cronin.

Cooper Laboratories, Wayne, New Jersey 07470 143-48



CARDIAC AUSCULTATION

18 multi-media modules present the physiological and clinical aspects of the normal and abnormal human heart

Each module consists of a *sound color film or videocassette, audiocassette,* a *set of slides,* and a *booklet.* The first module provides basic information on auscultation and the normal heart; each of the others is concerned with a specific cardiac lesion or group of lesions. Elements in a module complement one another, but *may be used independently.*

Films or videocassettes present heart sounds and murmurs in real time and slow motion, full-color diagrammatic animation of the heart, with synchronized sounds and murmurs, and simultaneous displays of pressure curves and sound notations.

Audiocassettes include auscultatory techniques, examples of auscultatory findings, exercises in discrimination, and interpretation with answers.

Slides include diagrams, examples of pathology, X-rays, angiograms, ECGs, and echocardiograms.

Booklets describe and illustrate hemodynamic changes and auscultatory features, etiology, pathology, physical signs, presentation, ECG, X-ray, echocardiographic features, history, and treatment.

Edited by **Alan Harris, M.D., M.B., M.R.C.P.; George Sutton, M.D., M.B., B.Chir., F.R.C.P.;** *and* **Malcolm K. Towers, M.B., B.Chir., F.R.C.P.;** *with a staff of international cardiologists; foreword by* **W. Proctor Harvey, M.D.**

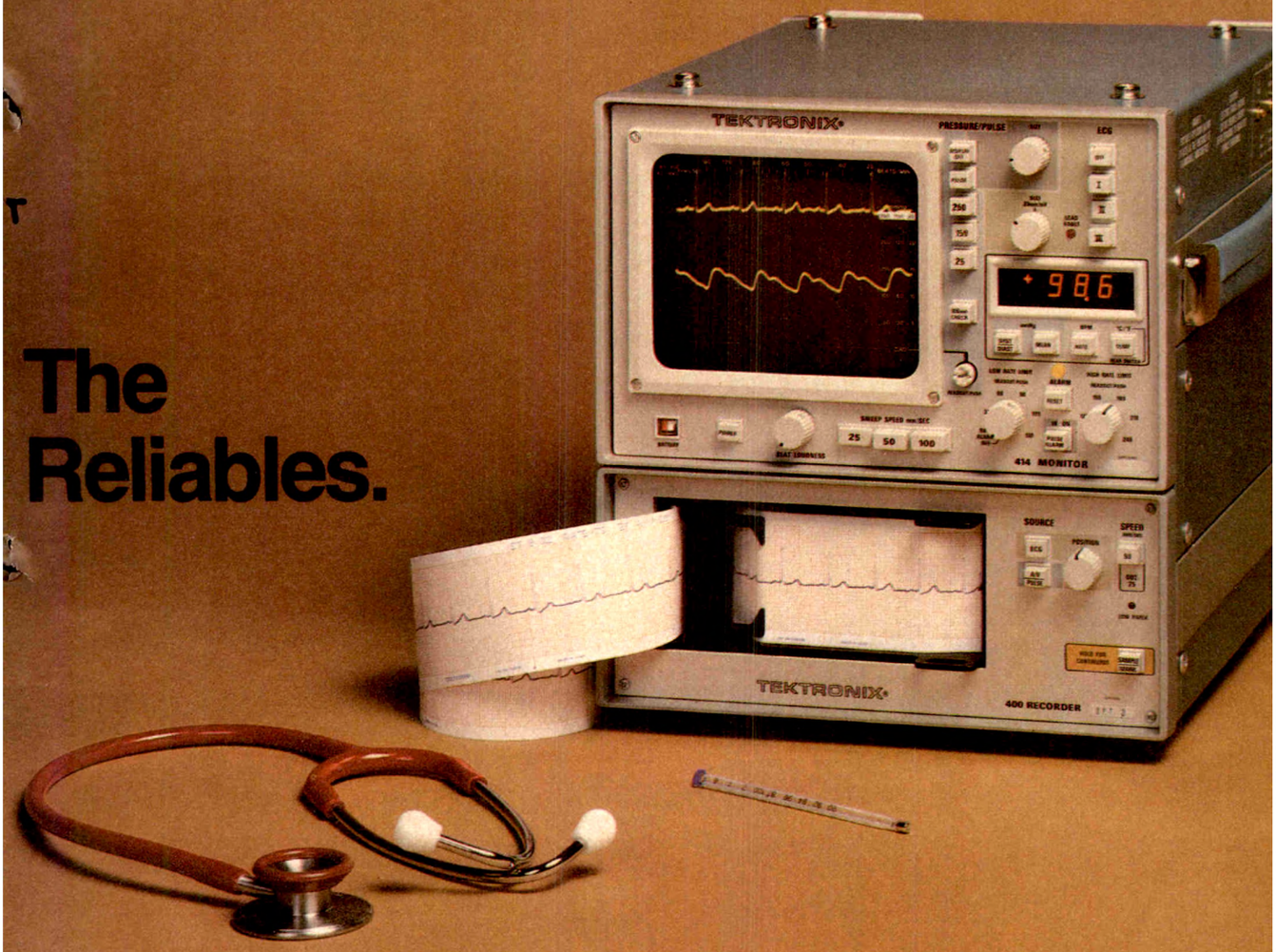
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Tektronix is a long-established corporate leader in the electronics industry with over $400 million in annual sales. Our reputation for product dependability has gone on the line with every monitor we've ever made. Today that reputation is stronger than ever.

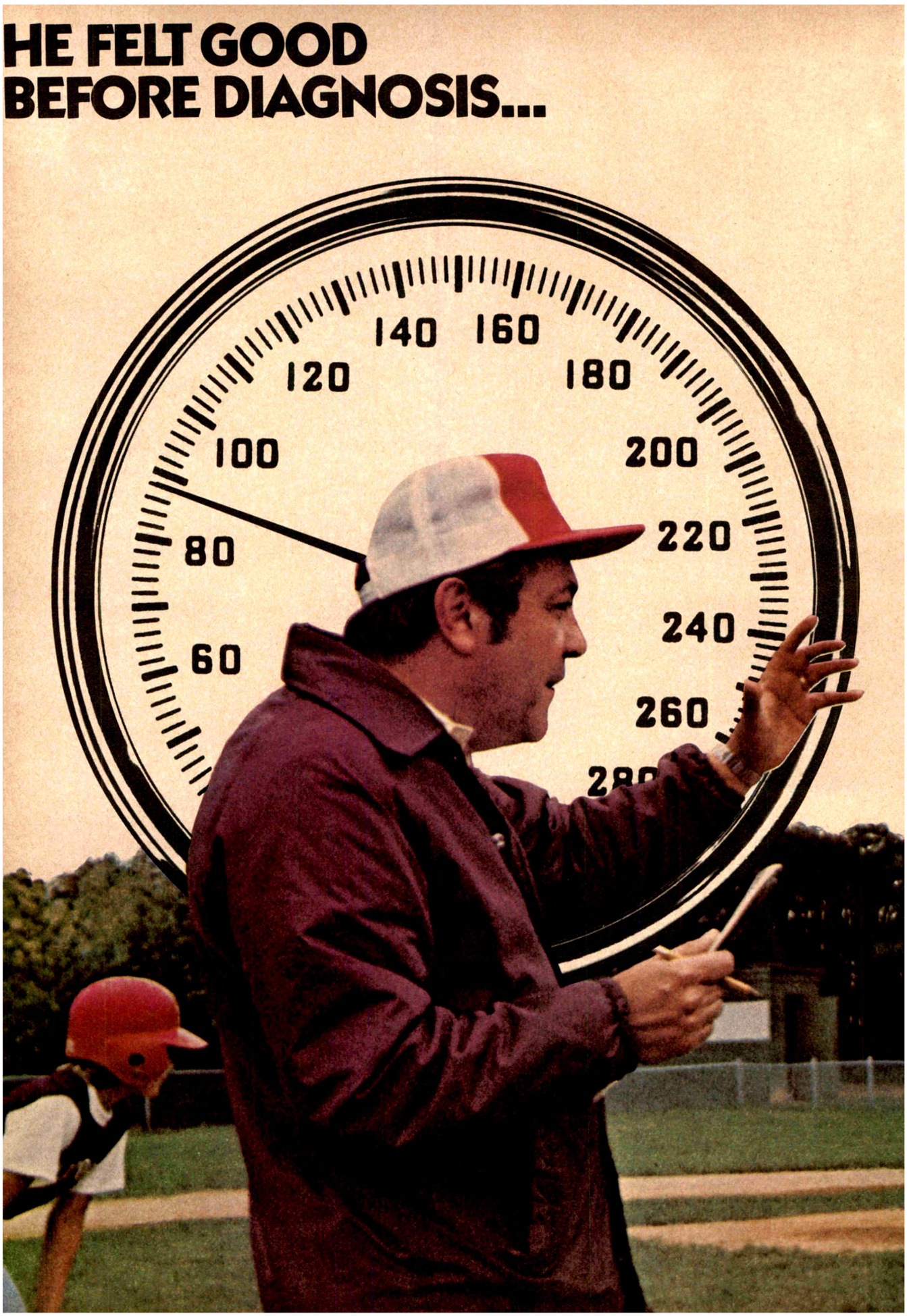
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Pictured above: The TEKTRONIX 414 Monitor with TEKTRONIX 400 Option 02 Recorder.

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...HE SH[illegible] FEEL [illegible] DU[illegible] IN[illegible]
THERAPY FOR HYPERTENSION*

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DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

TRIAMTERENE LIMITS POTASSIUM LOSS AS HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

It's difficult to make the asymptomatic patient feel better, but easy to make him feel worse. Potassium loss, a natural consequence of conventional diuretic/saliuretic activity, produces symptoms such as fatigue, malaise, and muscle cramps. Potassium-sparing triamterene in 'Dyazide' limits excessive potassium loss. Hypokalemia is seldom a problem with patients maintained on 'Dyazide'.

Convenient, economical for long-term control

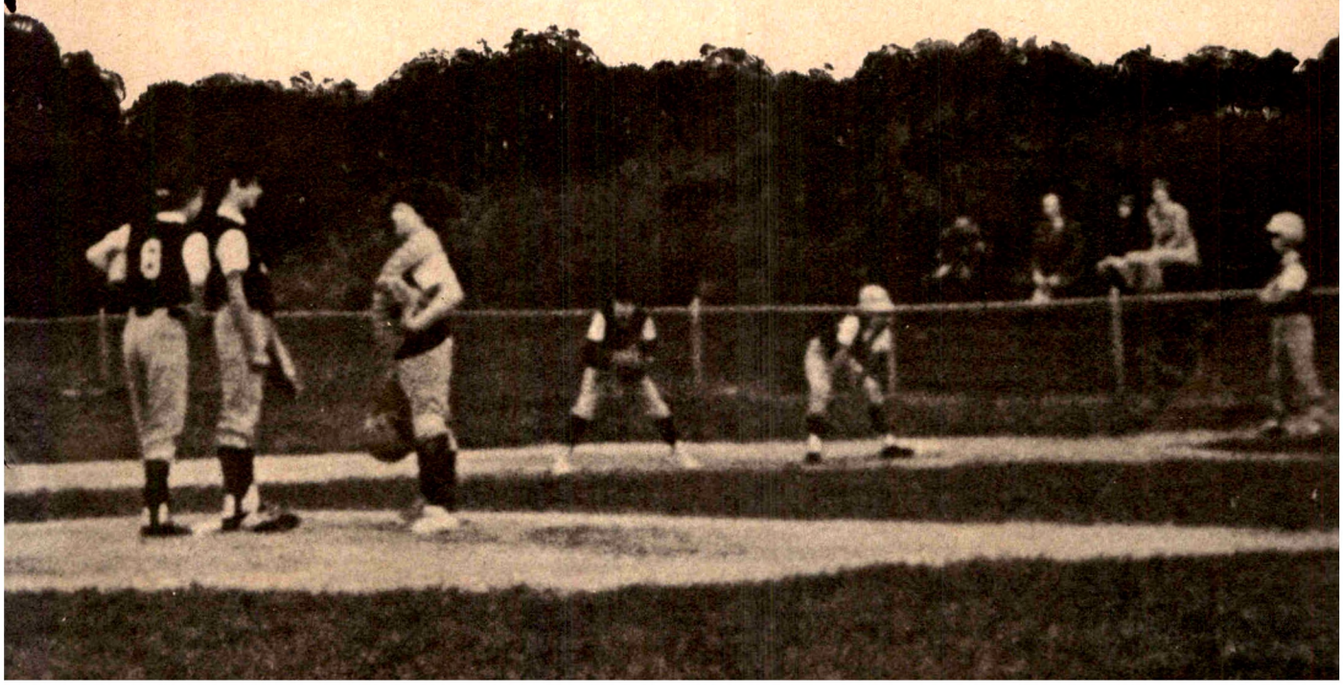
One or two capsules, once or twice daily for maintenance according to the response of the patient. Tedious, expensive K^+ rich diets or potassium salts should not be used unless hypokalemia develops or dietary K^+ intake is markedly impaired.

Serum K^+ and BUN should be checked periodically

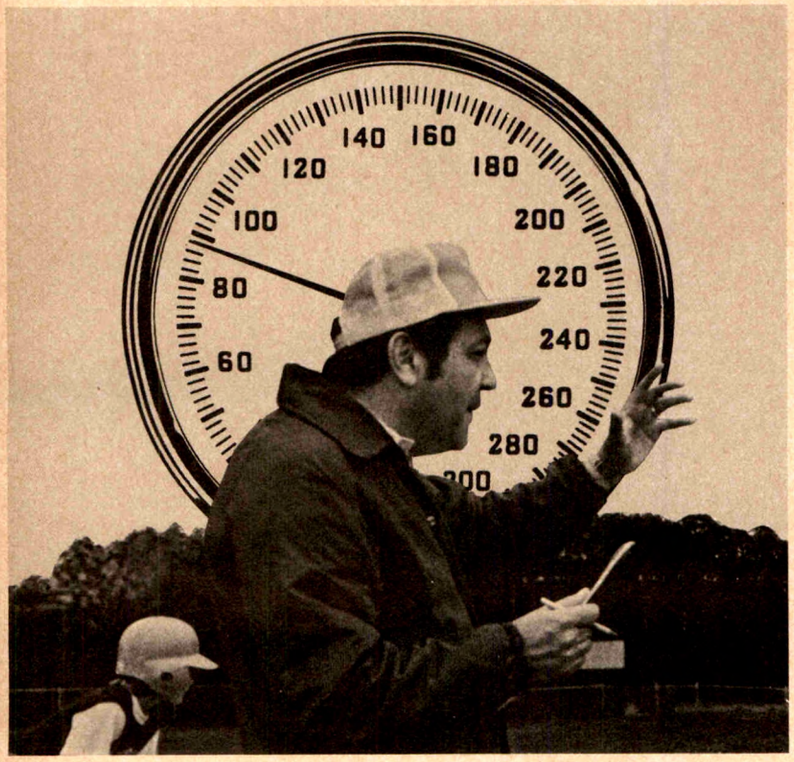
particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Elevated serum potassium levels can occur because of the K^+-sparing effect of triamterene, but they are rare in patients with normal renal function. If hyperkalemia develops, substitute a thiazide alone. Routine use of diuretics in healthy pregnant women is inappropriate.

*Not for initial therapy (see box warning). See next page for indications and brief summary of prescribing information.

SK&F CO.
a SmithKline company



FOR LONG-TERM CONTROL OF HYPERTENSION*



Trademark

DYAZIDE® MAKES SENSE

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

TRIAMTERENE LIMITS POTASSIUM LOSS AS HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE.

SK&F CO.
a SmithKline company

A106

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. A brief summary follows:

* WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

* **Indications:** When the combination represents the dosage determined by titration: Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, the nephrotic syndrome. Corticosteroid and estrogen-induced edema, idiopathic edema; hypertension, when the potassium sparing action of triamterene is warranted. (See Box Warning.) Routine use of diuretics in healthy pregnant women is inappropriate; they are indicated in pregnancy only when edema is due to pathological causes.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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American Egg Board

Announces 1978
Research Grants
For support of studies on the role of eggs in human nutrition and related basic problems.

Grants-in-aid will be made for research projects requiring one to three years, to non-profit institutions. Awards will be made on the basis of scientific excellence and pertinence to the research program of the American Egg Board and are subject to approval of the United States Department of Agriculture. Studies of the relationship of eggs and egg products in the diet to serum lipids and lipoproteins in man and to experimental atherogenesis in properly chosen animal models will be looked on with favor. Applicants must possess either the Ph.D. or M.D. degree.

The proposals submitted to the American Egg Board will be reviewed by a Scientific Review Panel for scientific excellence in competition with each other. This committee, serving as a study section, will critically review each application and record approval or disapproval. Those approved will be ranked according to a priority number ranging from 100 (highest) to 499 (lowest).

The Scientific Review Panel has been selected from a group of scientists active in biomedical fields relevant to the research program of the American Egg Board. Members are:

Elliott Rapaport, M.D., Chairman
Professor of Medicine
University of California, San Francisco
San Francisco General Hospital

Jack Geer, M.D.
Professor of Pathology
University of Alabama at Birmingham

Tavia Gordon, A. B.
National Institutes of Health
National Heart & Lung Institute

Antonio Gotto, M.D.
Professor of Medicine
Baylor College of Medicine
The Methodist Hospital

Scott Grundy, M.D.
Professor of Medicine
University of California, LaJolla and Veteran's Administration Hospital

Ralph Holman, Ph.D.
Professor of Biochemistry and Director of Hormel Institute
University of Minnesota

Adrian Ostfeld, M.D.
Lauder Prof. of Epidemiology and Public Health
Yale University School of Medicine

Robert Shank, M.D.
Professor of Preventive Medicine
Washington University School of Medicine

Application Deadline:
October 15, 1977

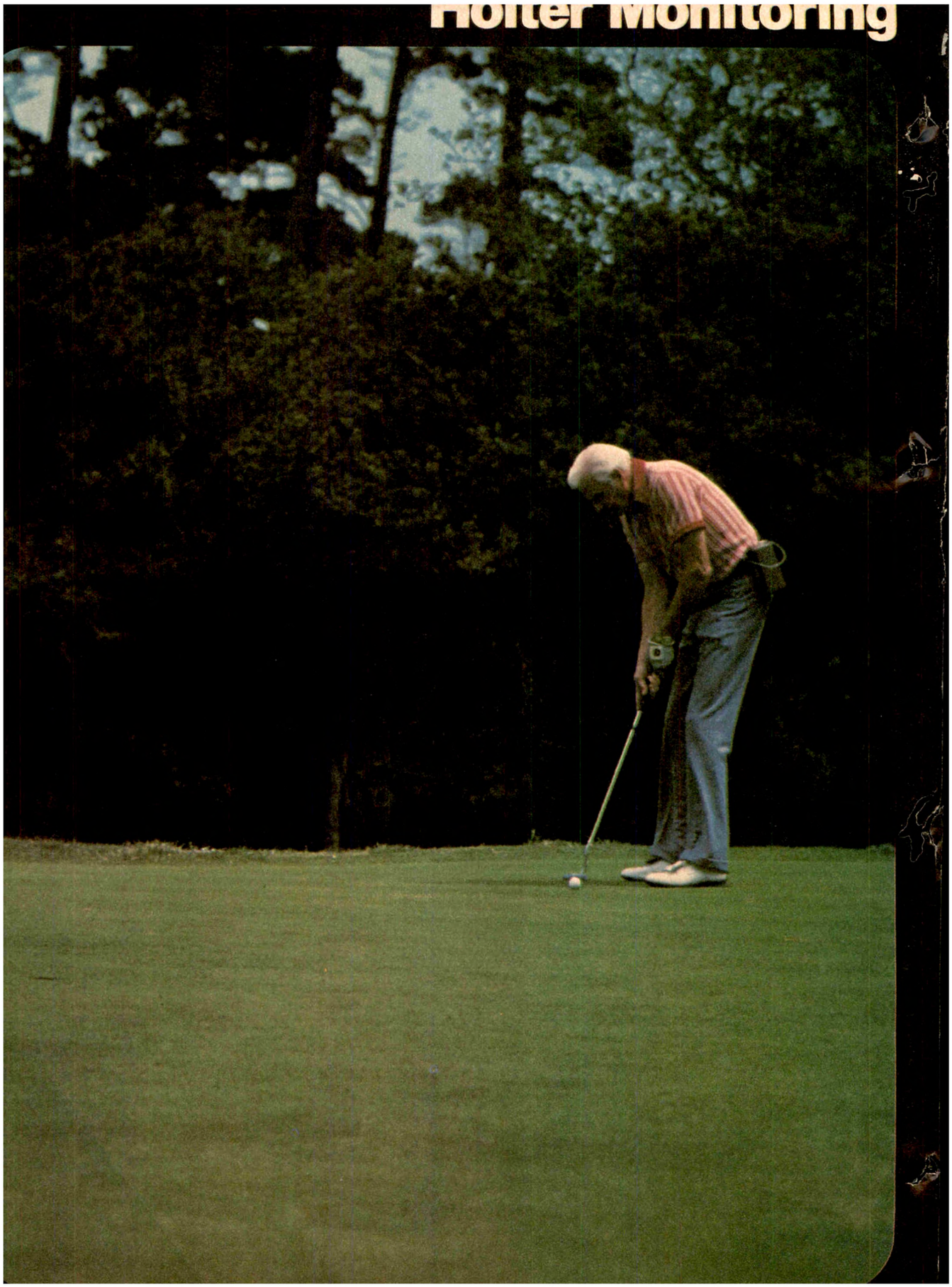
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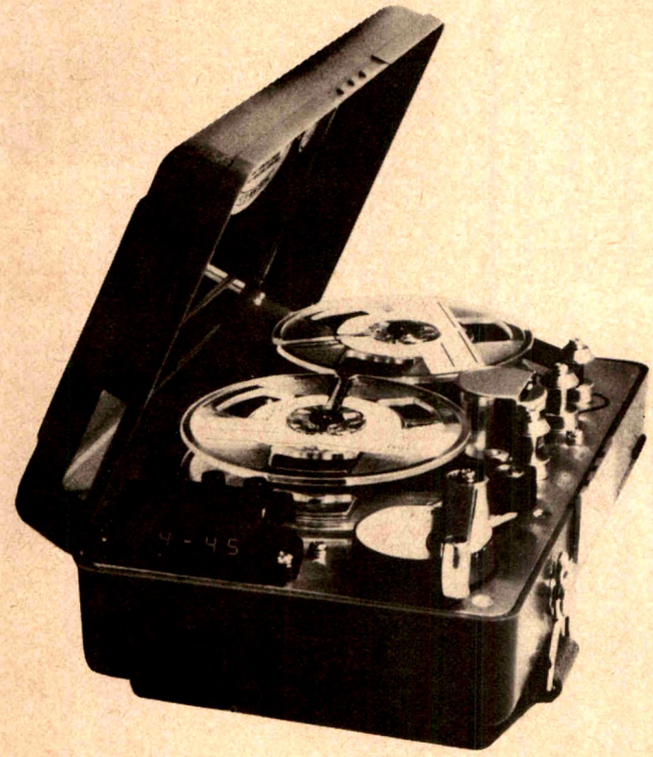


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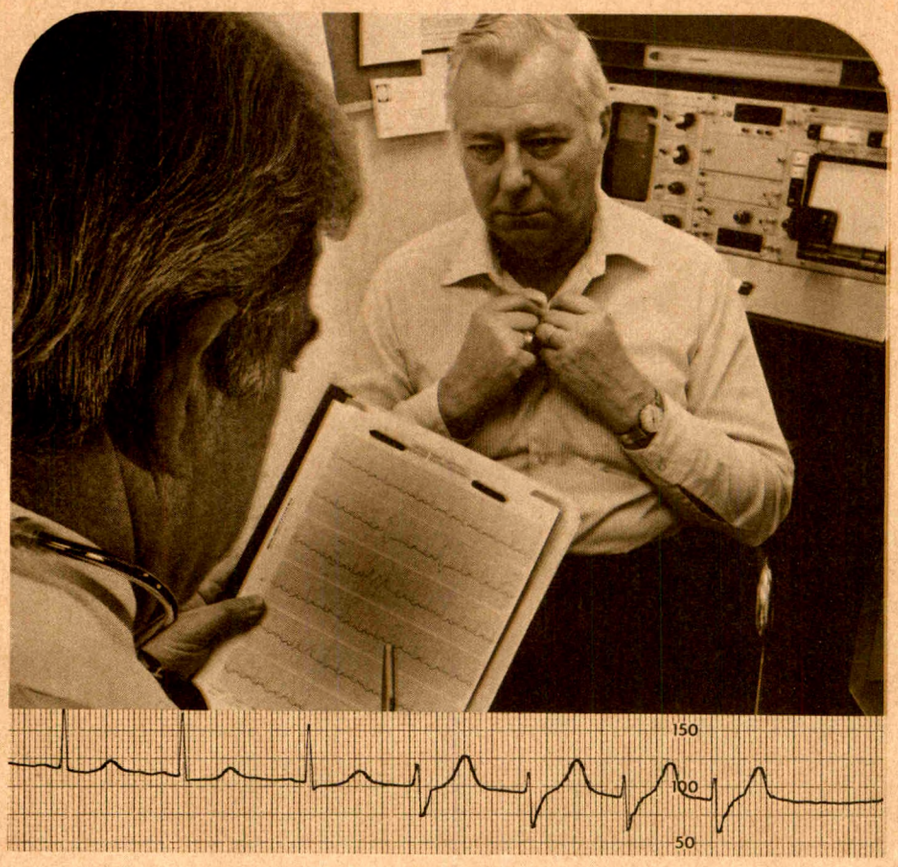
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Diagnosis: PVC's

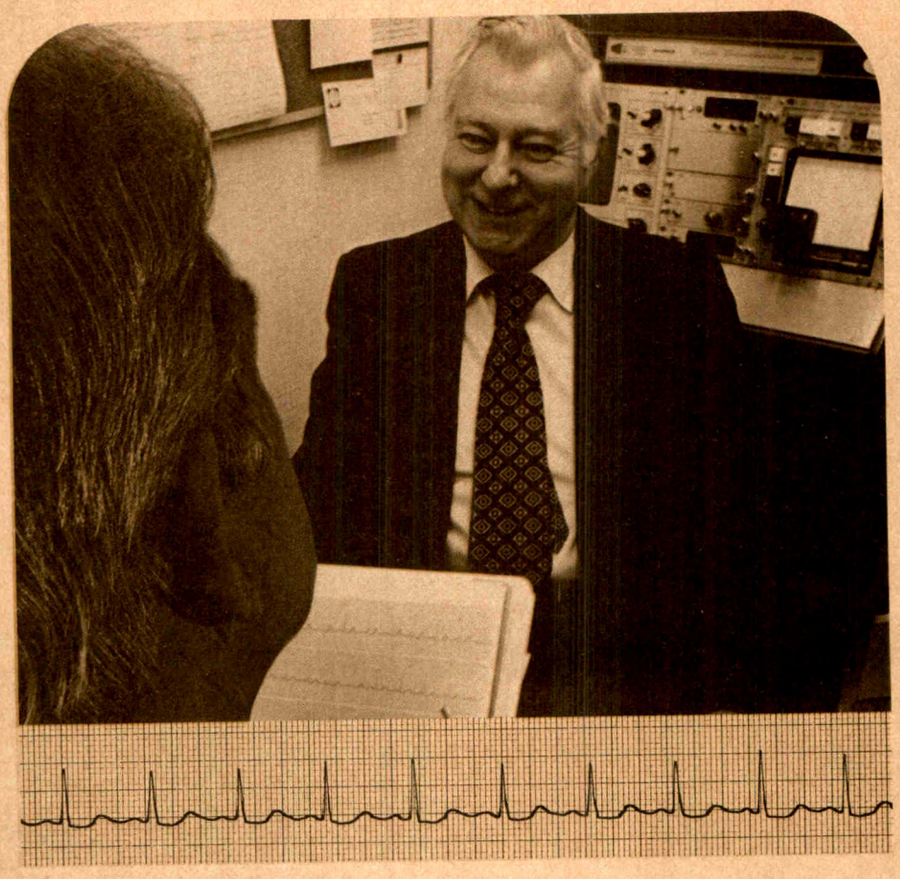
(Premature Ventricular Contractions)



initial therapy: quinidine sulfate tablets at

9 a.m.
1 p.m.
5 p.m.
9 p.m.

Then, to convenience and compliance...



a welcome change- simple q 8-12 hour dosage

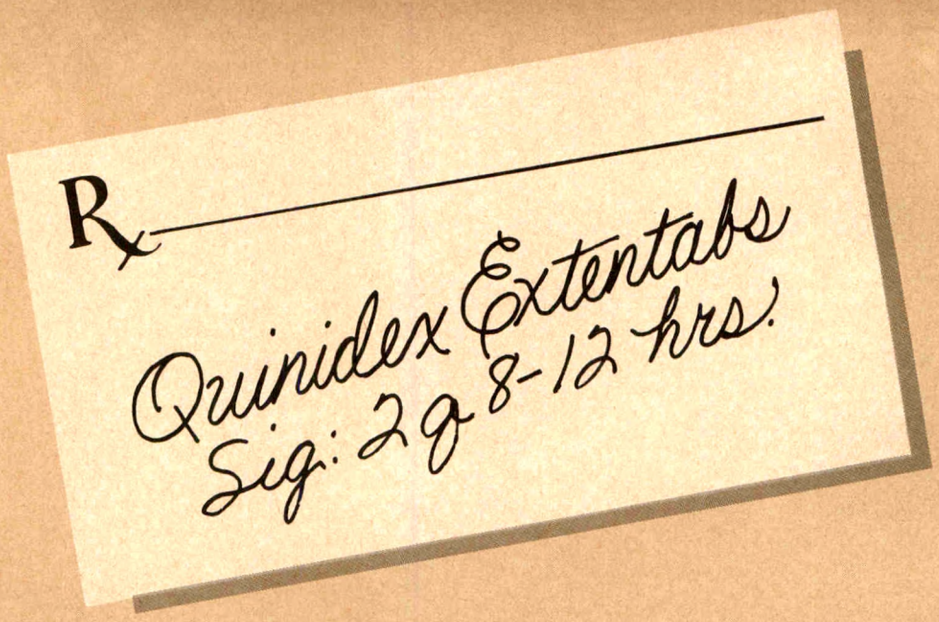
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(Quinidine Sulfate, USP)

After the PVC's have been successfully suppressed with quinidine sulfate tablets, you can *maintain* normal sinus rhythm with Quinidex Extentabs. The simple q 8-12 hour dosage is more convenient for the patient than the usual q.i.d. dosage for short-acting tablets. Instead of having to remember to carry his medication with him during the day, he simply leaves the bottle in the medicine cabinet. There's less risk of a missed dose . . . better compliance with your dosage regimen. The unique construction of Quinidex Extentabs provides continuous absorption of quinidine sulfate over an 8-12 hour period. Each of the Extentabs contains 300 mg quinidine sulfate-approximately 23% more quinidine alkaloid than 324 mg quinidine gluconate.

A·H·ROBINS

See full prescribing information on following page.



Indications:

Quinidex Extentabs are indicated in the treatment of:

Premature atrial and ventricular contractions.
Paroxysmal atrial tachycardia.
Paroxysmal A-V junctional rhythm.
Atrial flutter.
Paroxysmal atrial fibrillation.
Established atrial fibrillation when therapy is appropriate.
Paroxysmal ventricular tachycardia when not associated with complete heartblock.
Maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.

The only long-acting form of quinidine sulfate

Quinidex® Extentabs

ROBINS

(Quinidine Sulfate, USP)

A·H·ROBINS

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Contraindications: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity.

Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Warning: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting extremely rapid ventricular rate.

Precautions: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.

NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.

Adverse Reactions: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.

Dosage: Two Quinidex Extentabs every 8 to 12 hours.

How Supplied: White sugar-coated Extentabs in bottles of 100 and 250 (NDC 0031-6649).

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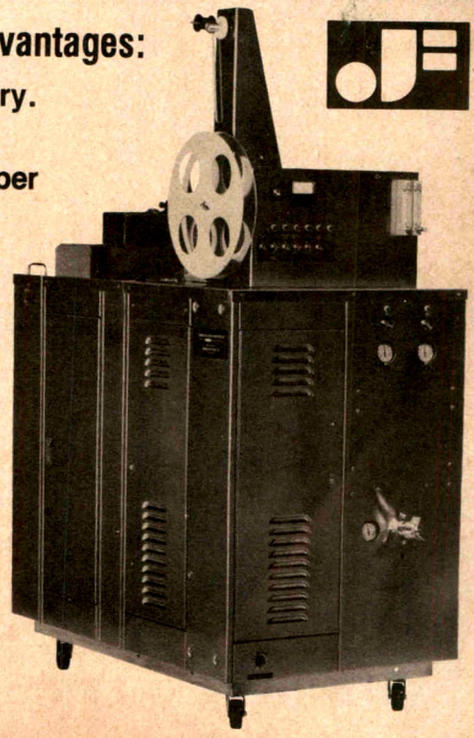
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Is their
cholesterol
control in
her hands?

evitably, it will be largely up to her as wife, mother, and ok, since dietary cholesterol control begins for the most rt at home and in the kitchen.

er new food program

tually, of course, her food planning begins in the gro- y store and at the meat counter. There, she will be nging her selections of family food—more chicken, veal, lean cuts of beef, no organ meats, fewer eggs, fat milk, corn oil margarine instead of butter, plenty egetables and fruit, and polyunsaturated oil such as n oil for cooking and salad dressing. A lot to member!

r motivation is a key to success

or another physician have told her husband that he a high serum cholesterol level, that it is a risk factor for nary heart disease, and should be reduced by dieting. t could be motivation enough. Keeping the family adwinner healthy can be the strongest of incentives. If has already had a coronary, he will probably accept ting with no need for further inducement. If he has er risk factors, hypertension can be dealt with by ı; giving up cigarettes and weight control are up to and can be solved.

udent dieting for the whole family?

at about the children? Familial hypercholesterolemia ears to be transmitted as an autosomal dominant trait. s, familial screening is indicated after finding one nber with the risk factor of high cholesterol. Moreover, ny American children have higher serum cholesterol els than other populations primarily due to the high ake of total calories, saturated fat, and cholesterol. nether or not normalizing the children's cholesterol els will substantially reduce risk of cardiovascular ease in later life, the chance is well worth taking. And n if their cholesterol levels are normal, promoting sent and future health is prudent practice.

elp for mother

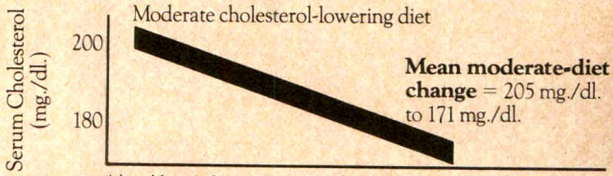
he family's new cholesterol-control diet, low in satu- at and cholesterol, mother must learn to read labels g a new food vocabulary—saturated, monounsatu- d and polyunsaturated fats, cholesterol, hydro- ted and partially hydrogenated vegetable oils, etc. to keep her family happy with the change in eating s, she will use new cooking techniques, recipes, and u ideas—such as those available from Mazola.®

ht 1977

Mazola® helps

Helps lower serum cholesterol

Results of an in-depth study exploring cholesterol-lowering diets



Adapted from Anderson, J.T., Grande, F., and Keys, A.: Cholesterol-lowering diets, J. Am. Diet. Assoc., 62:133, 1973.

In these trials, a standard diet was modified to produce a moderate cholesterol-lowering diet, using skim milk, lean meats, fish, two eggs a week, poultry, corn oil margarine, and Mazola® corn oil. The average decrease in serum cholesterol in 12 subjects in just three weeks was 17%. Serum phospholipids decreased 12%. Both changes were highly significant.

Helps diet adherence

For cholesterol control, long-term adherence is essential. To gain patient acceptance, the poly-unsaturated fats used must pass the test of taste. For flavor and lightness, Mazola corn oil and corn oil margarine qualify.



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A professional file of patient and physician aids for reduction of risk in atherosclerosis and coronary heart disease is now available free upon request. Included are five patient aids to help your patients live with a cholesterol-control diet and eight physician aids to help you evaluate and educate the high-risk patient.

Just mail this coupon to Mazola Nutrition Information Service, Dept. JRL-2, P.O. Box 307, Coventry, Conn. 06238.

NUTRITION INFORMATION SERVICE Mazola ™

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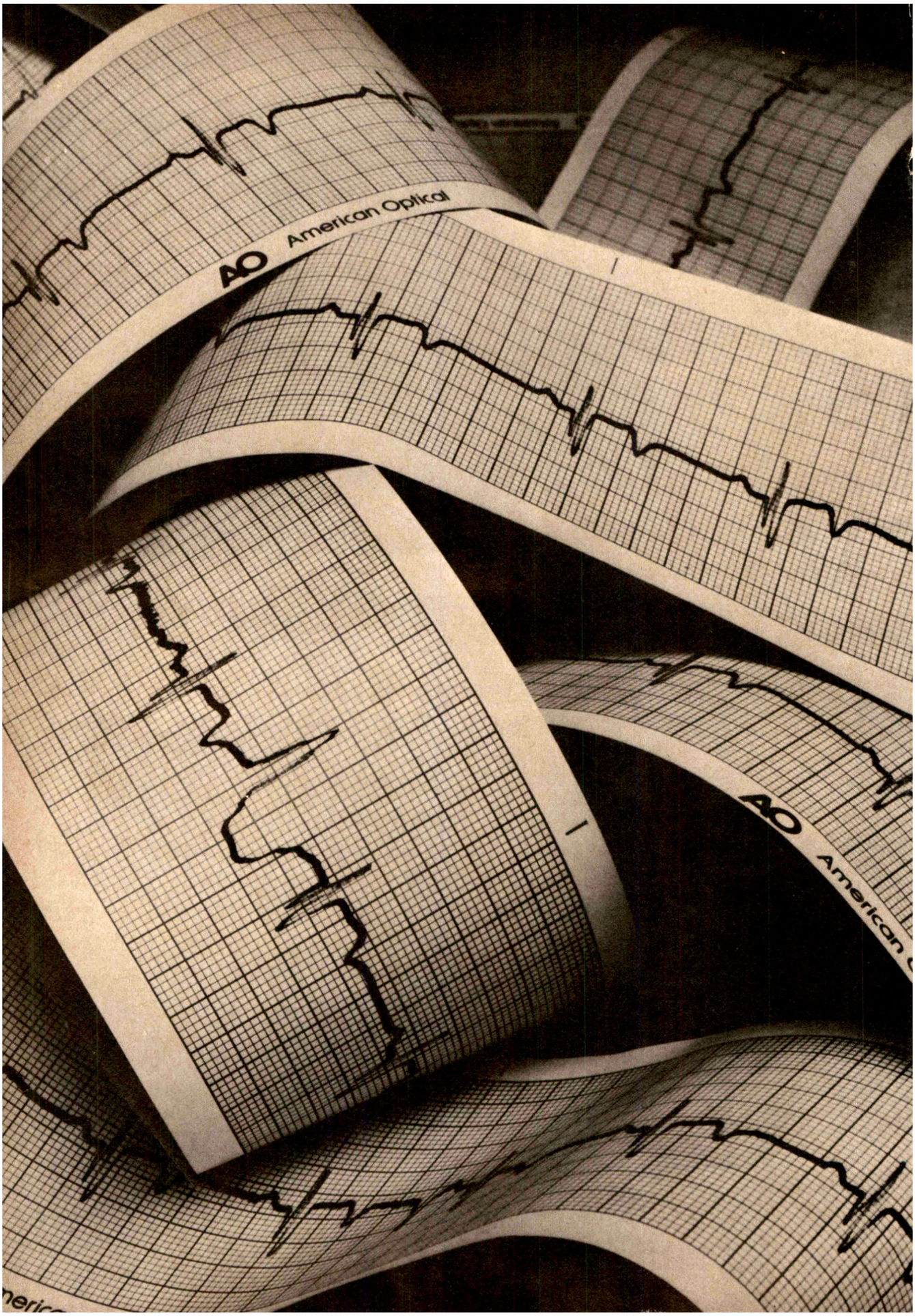
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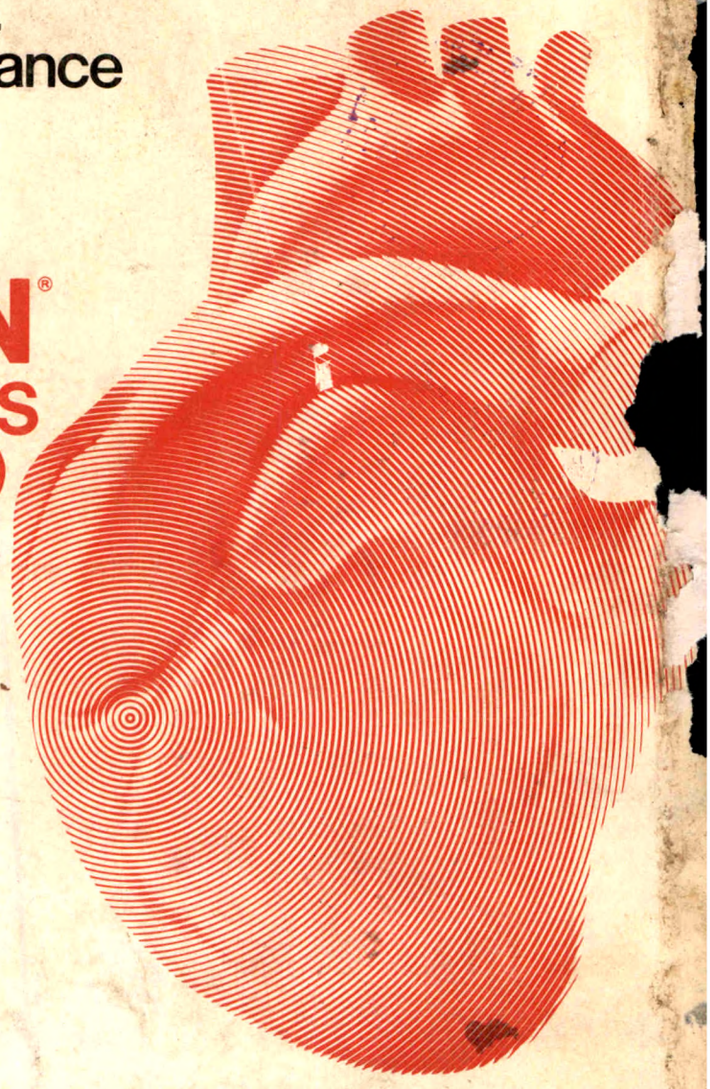
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CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance
- ☐ Full quinidine cardiodynamics
- ☐ Convenient B.I.D. or T.I.D. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases.

Well-tolerated, CARDIOQUIN Tablets are particularly suited for maintenance therapy, since the polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 50.

Purdue Frederick

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